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Original article

Development of second generation EP2 antagonists with high selectivity

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ABSTRACT

EP2 receptor has emerged as an important biological target for therapeutic intervention. In particular, it has been shown to exacerbate disease progression of a variety of CNS and peripheral diseases. Deletion of the EP2 receptor in mouse models recapitulates several features of the COX-2 inhibition, thus presenting a new avenue for anti-inflammatory therapy which could bypass some of the adverse side effects observed by the COX-2 inhibition therapy. We have recently reported a cinnamic amide class of EP2 antagonists with high potency, but these compounds exhibited a moderate selectivity against prostanoid receptor DP1. Moreover they possess acrylamide moiety in the structure, which may result in liver toxicity over longer period of use in a chronic disease model. Thus, we now developed a second generation compounds that devoid of the acrylamide functionality and possess high potency and improved (>1000-fold) selectivity to EP2 over other prostanoid receptors.

1. Introduction

Prostanoid receptor subtype EP2 has emerged as an important biological target, playing a protective as well as deleterious role in a variety of diseases [1,2]. EP2 activation has been shown to be beneficial in ischemic stroke and glaucoma models [3,4]. So far several agonists have been developed. A compound known as taprenepag isopropyl (PF-04217329) is undergoing phase-2 clinical evaluation for treating open-angle glaucoma and ocular hypertension [5,6]. A significant body of evidence suggests that EP2 plays a pro-inflammatory role in central nervous system (CNS) disorders including Alzheimer's disease (AD) [7], Parkinson's disease (PD) [8], amyotrophic lateral sclerosis (ALS) [9] and status epilepticus (SE) [10]; peripheral diseases such as rheumatoid arthritis (RA) [11], inflammatory bowel disease [12] and cancer [13–15]. Thus a highly selective antagonist for this receptor could be useful to develop treatments for these diseases. So far, a majority of the conclusions about the deleterious roles of EP2 are drawn from studies of EP2 knockout models, which also displayed salt-sensitive hypertension and infertility [16,17]. However, the data from pharmacological inhibition of this receptor are limited due to lack of selective EP2 antagonists until recently [18]. We recently reported a cinnamic amide class of EP2 antagonists which displayed high EP2 potency, but modest selectivity against a structurally close prostanoid receptor DP1 [19,20]. We now report several second generation EP2 antagonists with high potency and selectivity.

EP2, a Gαs-coupled receptor, is activated by the endogenous ligand PGE_2, produced by the cyclooxygenase enzymes (COX-1, COX-2). Upon activation, EP2 stimulates adenylate cyclase resulting in elevation of cAMP, which initiates downstream signaling by protein kinase A (PKA) or exchange protein activated by cAMP (Epac) [1,2,21,22].

2. Results and discussion

2.1. First generation EP2 antagonists show low selectivity, solubility and ADME properties

We recently reported a high-throughput screening campaign that indentified cinnamic amide **1** (a.k.a. TG4-155) as an initial hit (Fig. 1). We initially synthesized about 27 analogs for structure activity relationship study, which resulted in several compounds that displayed a high EP2 potency [20]. However, they showed modest (~10-fold) selectivity against a close member of prostanoid receptor DP1. Moreover, several compounds displayed low aqueous solubility and metabolic stability in microsomal fractions of mouse and human liver. Despite the low stability in liver microsomes, a trifluoroindole derivative of cinnamic amide (**2**, a.k.a. TG6-10-1) displayed a plasma half-life of 1.7 h, and brain-to plasma ratio of 1.7, and is currently used as a lead compound for proof of concept

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0223-5234/

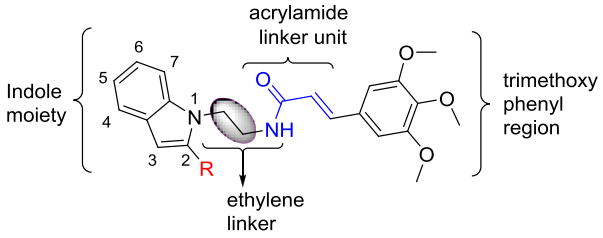


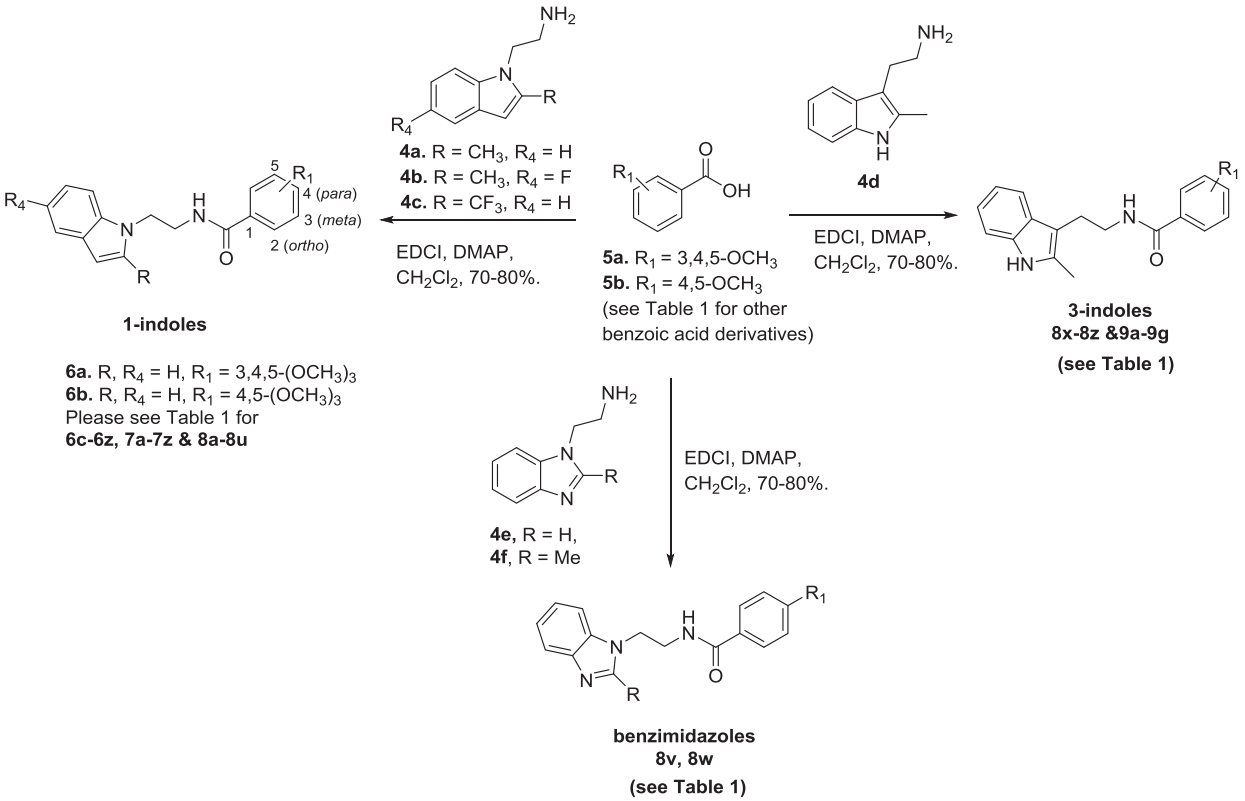
Fig. 1. Structures of first generation cinnamic amide EP2 antagonists [20].

studies [23]. Since then we synthesized 45 additional cinnamic amide derivatives to optimize the selectivity properties. From this, one compound TG8-21 displayed 181-fold selectivity to EP2 over DP1, but others showed <80-fold selectivity [19].

A majority of the first generation derivatives possess an acrylamide unit (Fig. 1), a structural moiety that mimics a Michael acceptor functionality, which is known to be reactive towards biologically active nucleophiles, potentially leading to off-target effects. To test this hypothesis, we first treated **2** (Fig. 1) with reduced glutathione (GSH) (3eq) in acetonitrile and water as a solvent system. However, this compound did not form any adduct with glutathione up until 72 h at ambient temperature. Furthermore, it was also not reacted by N-acetyl ethanethiol and a reactive morpholine, suggesting that the acrylamide in this class does not act like a Michael acceptor. In contrast, when we subjected the compound **2** to a reactive metabolite trapping test in human liver microsomes in the presence of NADPH and glutathione, it indicated the appearance of significant amount of glutathione adduct (+GSH-2H), in addition to other expected adducts (e.g. GSH + O−2H, GSH + O). This result suggests that this class of compounds might form reactive metabolites by liver metabolism [24]. However, when we tested the compound **2** for off-target activity against 47 ancillary targets that include several receptors, kinases and CYP450 enzymes, it displayed weak activity only against serotonin 5HT2A receptor with IC_{50} = 7.5 μM [23]. We did not explore any further to determine whether the GSH adducts are stemming solely from acrylamide moiety, but we speculate that this moiety might be a primary cause for the formation of reactive metabolites by this chemical class. Thus, we designed a second generation of analogs in this class that is devoid of the acrylamide moiety for further SAR study and selectivity characterization.

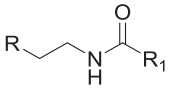
2.2. Synthesis of second generation amide EP2 antagonists

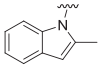
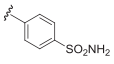
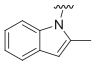
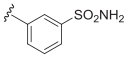
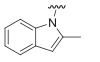
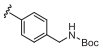
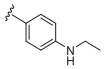
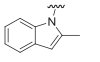
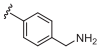
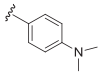
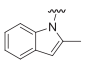
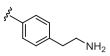
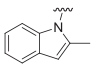
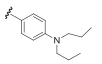
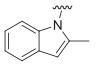
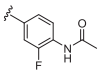
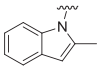
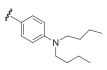
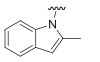
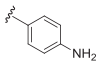
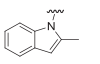
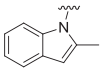
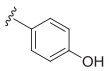
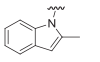
Earlier structure activity relationship (SAR) study on 1 indicated that the acrylamide moiety is optimal, but not essential for EP2 bioactivity [19,20]. The derivatives that are devoid of the acrylamide moiety, for example **3** (Fig. 1) displayed EP2 Schild potency of 214 nM, a 90-fold smaller potency than **1** [19,20]. Thus, we envisioned synthesizing a variety of a second generation analogs by shrinking the acrylamide to an 'amide' linker for further SAR study. We first synthesized amide derivatives **6a** and **6b** as shown in Scheme 1, starting from 2-(2-methyl-1*H*-indol-1-yl)ethan-1-amine (**4a**) and 3,4,5-trimethoxybenzoic acid (**5a**) and 3,4-dimethoxybenzoic acid (**5b**). The other substituted derivatives on the phenyl ring (**6c**–**z**, **7a**–**z**, & **8a**–**u**), isomeric 3-inodole derivatives (**8x**–**z,** & **9a**–**g**), and imidazole derivatives ((**8v**–**w**) were synthesized analogous to **6a** and **6b** as illustrated by the general Scheme 1 (Table 1 for individual structures).



Scheme 1. Synthesis of second generation amide EP2 antagonists for SAR study. EDCI = 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride; DMAP = dimethylaminopyridine.

Table 1
Structures and bioactivity of second generation EP2 antagonists.[a]



Entry	Compd. ID	R	R1	EP2 K_B (nM)	Entry	Compd. ID	R	R1	EP2 K_B (nM)
6a	TG7-112-1			>1000	**6v**	TG7-161			486
6b	TG7-112-2			22.3	**6w**	TG7-165			>1000
6c	TG7-224			75.6	**6x**	TG7-254			84
6d	TG7-237			15.5	**6y**	TG7-258			690
6e	TG7-142			9.8	**6z**	TG7-272			1220
6f	TG7-171			2.7	**7a**	TG7-164			18.1
6g	TG7-192			11.9	**7b**	TG7-158			530
6h	TG7-188			68.8	**7c**	TG7-225			86.8
6i	TG7-143			210	**7d**	TG7-206			4.6
6j	TG7-223			>1000	**7e**	TG7-213			310
6k	TG7-179			>1000	**7f**	TG6-201			20.2
6l	TG7-205			62.9	**7g**	TG7-214			61.2
6m	TG7-233			150	**7h**	TG7-155-1			140
6n	TG7-117			97	**7i**	TG7-155-2			280
6o	TG7-157			51	**7j**	TG7-173			24.7
6p	TG7-140			150	**7k**	TG7-152			9.4
6q	TG7-227			>1000	**7l**	TG7-240			30.3
6r	TG7-226			800	**7m**	TG8-24			500
6s	TG7-147			140	**7n**	TG8-29			89.7

(*continued on next page*)

Table 1 (*continued*)

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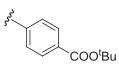
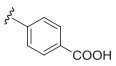
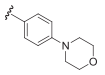
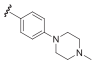
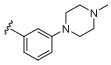
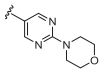
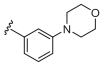
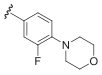
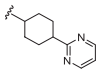
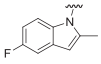
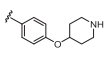
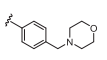
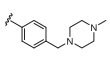
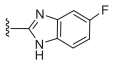
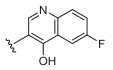
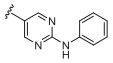
6t	TG7-172			100	**7o**	TG7-185			22.6
6u	TG7-176			245	**7p**	TG7-170			9.6
7q	TG7-166			64	**8n**	TG7-229			57.8
7r	TG7-255			770	**8o**	TG7-249			76.5
7s	TG7-256			>1000	**8p**	TG7-259			520
7t	TG7-153			25.7	**8q**	TG7-244			380
7u	TG7-141			45	**8r**	TG7-183			14.9
7v	TG7-182			148	**8s**	TG7-184			62.2
7w	TG7-180			26.8	**8t**	TG7-194			150
7x	TG7-159			42.2	**8u**	TG7-195			120
7y	TG8-8			32.2	**8v**	TG7-199			190
7z	TG8-15			22.3	**8w**	TG7-203			>1000
8a	TG7-178			20.9	**8x**	TG7-146			138
8b	TG7-193			120	**8y**	TG7-231			>1000
8c	TG7-202-2			410	**8z**	TG7-167			10.8
8d	TG7-211			50.2	**9a**	TG7-181			6.9
8e	TG7-257			87.5	**9b**	TG7-168			19.8
8f	TG7-207			84.1	**9c**	TG7-174			28.6
8g	TG7-264			95	**9d**	TG7-175			66
8h	TG7-268			>1000	**9e**	TG7-169			135

Table 1 (*continued*)

Entry	Compd. ID	R	R1	EP2 K_B (nM)	Entry	Compd. ID	R	R1	EP2 K_B (nM)
8i	TG7-234			>1000	**9f**	TG7-232			155
8j	TG8-5			970	**9g**	TG8-9			280
8k	TG8-5			>1000	**9h**	TG7-118			130
8l	TG7-261			>1000	**9i**	TG7-148			175
8m	TG7-228			1.6	**9j**	TG7-120			>1000

[a] Schild K_B values are calculated using the formula log (dr-1) = log X_B − log K_B, where dr (dose ratio) = fold shift in EC_{50} of PGE_2 by the test compound, X_B is antagonist concentration [1 μM]. K_B value indicates a concentration required to produce a 2-fold rightward shift of PGE_2 concentration response curve. K_B values are average of 2–3 measurements run in duplicate.

2.3. Second generation analogs show low nanomolar EP2 potency and high selectivity index

More than 92 amide derivatives have been synthesized and evaluated for inhibitory potency on PGE_2-mediated EP2 activation by measuring the Schild K_B (Table 1). Interestingly, the 3,4,5-trimethoxyamide derivative **6a** showed no EP2 activity, where as the 4,5-dimethoxyamide derivative **6b** displayed strong EP2 potency (Schild K_B = 22 nM). Thus, we used **6b** as a lead for the synthesis of other second generation amide derivatives. As shown in Table 1, we first focused on derivatising the phenyl group with a variety of electron donating or withdrawing groups at various positions (*ortho*, *meta* and *para*). We describe the potency of these analogs in rank order in comparison to the 3,4-dimethoxyderivative **6b.** For example, a compound with a single methoxy group at the *para*-position (**6c**) showed 3.4-fold less potency than dimethoxyderivative (**6b**), and a compound with *para*-ethylamino group (**6d**) displayed nearly same activity as **6b.** Interestingly, a *para*-dimethylaminoamide (**6e**), or *para*-diethylaminoamide (**6f**) exhibited about 2-fold or 8-fold improved EP2 potency respectively in comparison to **6b.** Then we examined amides with lengthy alkyl groups such as two propyls (**6g**) and two butyls (**6h**), but they indicated that ethyl group is optimal for activity, because increasing the length of alkyls gradually decreases the potency (Table 1). Nonetheless, the dipropylamino derivative displayed 2-fold higher potency than **6b.** The unsubstituted amine derivative (**6i**) showed reduced potency by 9-fold, and the derivatives with hydroxyl group (**6j**) and guanidine group (**6k**) displayed loss of potency, suggesting this region may have been exposed into a hydrophobic region on the EP2 receptor. We then explored several electron withdrawing groups at the same *para*-position of the phenyl ring. For example, an acetoxyderivative (**6m**) showed 6.7-fold less potency, an N-acetyl-derivative (**8n**) showed a 4-fold less and an N-benzoyl derivative (**8o**) showed 2-fold less in comparison to **6b.** Moreover, an acetamide derivative (**6p**) showed about 6.7-fold less, and a dimethylacetamide (**6q**), diethylacetamide (**6r**) showed 58-fold and 35-fold less potency than **6b**, respectively. Likewise, a cyano derivative (**6s**), and a tert-butylcarbaoxylate (**6t**) showed decreased potency by 6.2 and 4.4 −fold, respectively. A carboxylic acid group (**6u**) also reduced EP2 potency (245 nM), suggesting electron donating groups enhance the EP2 potency whereas the withdrawing groups, at *para*-position of the phenyl ring, decrease potency (Table 1).

We also synthesized and tested analogs with additional groups such as fluorine, trifluoromethyl, and methoxyl at the other positions (ortho (*o*), meta (*m*) and para (*p*)) of the phenyl to see any additional advantages to the potency, but mostly these groups either reduced the potency or brought no changes in comparison to the compounds without these groups. For example, a fluorine at *m*-position, next to alkylamino group, reduced the potency about 2-fold (*cf.* **7a vs. 6e; 7d vs. 6f**), but a fluorine at the same position had no effect on *p*-cyano derivative (**7h vs. 6s**) and a *p*-methoxy derivative (**7c vs. 6c**), but moving the fluorine from *m*-position to *o*-position reduced the EP2 potency (**7i vs. 7h**). Likewise, a trifluoromethyl group next to *p*-ethylamino group had no impact on the EP2 potency (**7f vs. 6d**), but this group resulted in 113-fold reduced potency on *p*-diethylamino derivative (**7e vs. 6f**). Moreover, a methoxyl group at *m*-position also reduced the potency by 22-fold (*cf.* **7g vs. 6f**), suggesting single substitution only at *p*-position of the phenyl is optimal for EP2 activity, and additional groups at other positions decrease the EP2 potency. We also tested compound with a sulfonamide at *p*-position on the phenyl ring, this group also reduced the potency by 21-fold (**6v vs. 6b**), and the same group at *m*-position resulted in loss of potency (**6w vs. 6b**), reinforcing the above assertion that substitution at *p*-position is optimal, but at *m*-position, it is detrimental to the EP2 potency (Table 1).

We then explored derivatives in which the nitrogen heteroatom is connected to the phenyl ring with extra methylene group to determine whether *p*-amino (to the amide group) is essential for EP2 potency. For example, a *p*-methylamine derivative (**6y**) showed about 3-fold less potency than *p*-amino derivative (**6i**) and a compound with two methylene groups between phenyl and amine (**6z**) displayed 6-fold less potency than the *p*-amine derivative (**6i**), suggesting alkylamino groups directly attached to phenyl ring provide optimal EP2 potency than the ones that are away from the phenyl ring. Interestingly however, a *tert*-butylcarboxylate protected *p*-methylamino derivative (**6x**) showed 2.4-fold higher potency than the free *p*-amino derivative (**6i**) (Table 1).

We then synthesized and examined a variety of nitrogen heterocyclic rings at the *p*-position of the phenyl ring. Pyrrolidine (**7j**) and homopiperidine (**7o**) derivatives showed approximately equal potency to **6b**. However, a piperidine derivative (7**k**) and a morpholine derivative (**7p**) both displayed about 2.3-fold higher EP2 potency than **6b** (Table 1). Furthermore, we also synthesized and tested analogs with a methyl group (**7l**) and an ethylester (**7m**) and carboxylic acid (**7n**), hydroxyl group (**7w**) on the piperidine ring. Interestingly, while the ethylester piperidine derivative (**7m**) showed 20-fold less, a carboxylic acid displayed 4-fold less activity to **6b**, and a hydroxylpiperidine derivatives displayed nearly equal

EP2 potency as **6b** (Table 1), indicating hydrophilic groups on the piperidine ring will help to maintain the EP2 potency. Likewise, a methylpiperazine (**7q**), or a methylhomopiperizine ring (**7v**) at *p*-position of the phenyl ring also resulted in 2.8-fold or 6.6-fold loss of potency, in comparison to **6b**. We then explored SAR by moving these heterocyclic rings from *p*-position to *m*-position. But this strategy resulted in less active compounds in comparison to *p*-substituted derivatives (*cf.* **7s** *vs.* **7p**; **7r** *vs.* **7q**). Likewise, incorporation of fluorine atom at *m*-position on the phenyl ring (next to the heterocyclic rings) showed a trend towards increasing the potency in one case (*cf.* **7u** *vs.* **7q),** but decreased the potency by 2-fold in other (*cf.* **7t** *vs.* **7p**), reinforcing the suggestion (*vide infra*) that a single group at *p*-position provides optimal higher EP2 potency.

We further explored other heterocyclics at the *p*-position of the phenyl ring (**7x**–**z**), and few benzofused heterocyclics (**8a, 8e** and **8f**) for SAR study. The 1-tetrazoles **7x** and **7y** displayed 1.5–2-fold less potency, but the 5-tetrazole (**7z**) and the benzofused-imidazole (**8a**) displayed equal potency to **6b**, whereas the benzofused-triazole (**8e**) and benzofused-quinazoline (**8f**) both displayed 4-fold reduced potency in comparison to **6b.** Interestingly, a cyclohexane ring at *p*-position (**8b**) showed 5.5-fold less potency in comparison to **6b**, suggesting nitrogen in the ring helps maintain the potency at <100 nM, but a heteroatom is not absolutely essential for full bioactivity. Again a strategy to extend these heterocyclic rings with an extra methylene group or oxygen atom resulted in loss of potency (see **8i**–**k**), reinforcing the notion that direct nitrogen attachment to the phenyl ring will improve potency (Table 1).

We also envisioned synthesizing compounds with a pyrimidine ring replacing the phenyl ring, then exploring substitutions on this ring. As shown in Table 1, a 2-aminopyrimidine-amide (**8l**) displayed loss of potency, in comparison to an equivalent **6i** which displayed EP2 potency of 210 nM. However, a 2-ethylamino derivative (**8n**) or, 2-morpholino derivative (**8o**) showed EP2 potency of 58 and 76.5 nM, respectively. These potencies are 4–8-fold less than their equivalents **6d**, **7p**. In contrast, a 2-phenylamino derivative exhibited a higher EP2 potency (Schild K_B = 1.6 nM). Moreover, we also examined compounds in which the phenyl ring is replaced by a nicotinamide ring (**8p**), and a pyrimidine substituted cyclohexane ring (**8q**), but both these derivatives displayed about 20-fold less potency in comparison to **6b**, suggesting phenyl or pyrimidine rings are optimal for high EP2 potency. Furthermore, we synthesized and tested additional heterocycles such as imidazole (**9h**), 4-hydroxyquinoline (**9i**), and pyrrolidine (**9j**), replacing the phenyl ring. However, 2-imidazole derivative **9h**, 2-quinoline compound **9i** showed weak EP2 potency (K_B = 128 nM, 174 nM respectively), and the pyrrolidine derivative (**9j**) displayed loss of potency. These results suggest further modifications on this phenyl region may yield compounds with enhanced bioactivity.

Having identified several compounds with EP2 potency <50 nM with modifications on the right side phenyl ring, we explored the left side indole ring to determine whether any enhancement to the potency is possible. Blocking the *ortho*-, and *para*-positions to the indole ring nitrogen could potentially limit metabolic oxidation of the scaffold. Thus we have synthesized two compounds (**8r** and **8s**) with fluorine at 5th position of the indole ring (Table 1). Interestingly, these two compounds displayed similar potencies in comparison to the unsubstituted derivatives (**8r** *vs.* **7p**; **8s** *vs.* **7u**), but we have not yet explored the *o*-position to the indole nitrogen due to lack of available starting materials for synthesis. From our earlier SAR on the first generation analogs, we learned that only limited modifications (e.g. CF_3) are allowable at 2nd position of the indole ring with about 10-fold loss of potency (*cf.* **1** *vs.* **2**) [20]. Thus, we only synthesized a few analogs with a trifluoromethyl group at 2nd position. As shown by two examples, **8t** and **8u** (Table 1), the trifluoromethyl group at 2nd position resulted in 12–54-fold less EP2 potency in comparison to a methyl group at the same position (**8t** *vs.* **6f**; **8u** *vs.* **7p**). We also synthesized analogs with imidazole ring in place of indole ring with premise that an extra nitrogen in the imidazole ring offers additional drug like features, including enhanced solubility and metabolic stability by blocking the 3rd position, where this position seems to liable in the case of indoles [25]. However, an imidazole derivative (**8v**) showed a 70-fold less potency than its indole equivalent compound (**6f**). One point is noteworthy here. In the earlier study, we observed that a methyl group at 2nd position of the indole ring accelerates metabolism in liver fractions compared with a trifluoromethyl group [20]. Thus, we synthesized analogs without a methyl group at 2nd position of the indole (**6l**), and imidazole ring (**8w**). However, the indole derivative without methyl group (**6l**) was found to be 23-fold less potent than its methyl equivalent (**6f**), and the imidazole derivative without methyl group (**8w**) displayed complete loss of EP2 potency, reinforcing the observation that methyl is very important for high EP2 bioactivity (Table 1).

We then examined isomeric 3-indole derivatives (**8x**–**8z, 9a**–**9g**) for SAR study. As shown in Table 1, the 3-indole isomeric derivatives showed nearly equal potency to their 1-indole equivalent compounds (*cf.* **8x** vs.**6n**; **8y** vs. **6r**; **8z** vs. **6e**; **9a** vs. **6f**; **9b** vs. **7k**; **9c** vs. **7p**; **9d** vs. **7t**; **9e** vs. **7q**), suggesting both 1-indole and 3-indole derivatives are, in general, are potent antagonist of EP2 receptor and useful for further development of EP2 drugs.

Finally, we explored the linker region for SAR study. Extension of the chain from two carbons to three carbons, as illustrated by the indolepropane amide (**9k)**, constraining the linker as in derivatives **9l** and **9m** (Fig. 2) resulted in loss of potency in comparison to their shorter equivalents (**6f** and **7p**). Moreover, we also synthesized an ester analog (**9n**) to determine whether the amide bond is necessary for EP2 potency. This analog resulted in loss of potency, indicating that the amide is crucial for the EP2 bioactivity.

Overall, the SAR study indicates a dialkylaminogroup or nitrogen heterocycles at *p*-position, a methyl group at 2nd position of indole ring, and an ethylamine linker are optimal for high EP2 potency. The compounds **6f, 7p, 7z, 8z, 9a** and **7k, 7p** display high EP2 potency, with Schild K_B approximately 10 nM. However, several other compounds (Table 1) displayed EP2 potency below 100 nM, and a variety of heterocycles retains a modest EP2 potency, suggesting these scaffolds could be further refined into highly potent antagonists for the EP2 receptor.

2.4. Characterization of selectivity against other prostanoid receptors

The EP2 receptor is a member of the prostanoid receptor family and shares 20–30% structural homology with EP1, EP3 and EP4, all

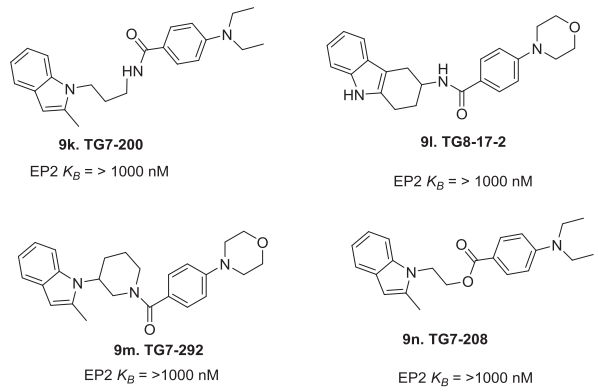


Fig. 2. Structures of additional analogs synthesized for SAR study. Structural modifications are made to the linker region in these derivatives.

of these are activated by a common agonist PGE_2. However, EP2 exhibits the highest amino acid homology to DP1 (44%) and IP (40%) receptors, which are activated by PGD_2 and PGI_2 respectively [26–28]. Furthermore, studies indicate that DP1 has similar physiological functions as EP2 [27], whereas the activation of the IP receptor is shown to be important for cardioprotection [29,30]. EP2, EP4, DP1 and IP are all Gαs-coupled transmembrane receptors [27]. Thus we examined the selectivity of the novel EP2 antagonists mainly over EP4, DP1 and IP. We selected and tested several highly potent second generation amide EP2 antagonists that showed EP2 $K_B \leq 50$ nM. Interestingly, these amide derivatives showed much improved selectivity in comparison to the first generations derivatives. For example, **6f** displayed >1200-fold selectivity against DP1 receptor (Table 2), compound **6e** displayed 655-fold, and **7j** and **7p** showed 516-fold and 533-fold selectivity over DP1 respectively. Moreover, compounds **6g, 7k,** and **10z** displayed over 275-fold selectivity against DP1.

We then examined several of these compounds against EP4 and IP receptors at single concentration of 10 μM. The extrapolated Schild K_Bs for these receptors are shown Table 2. A vast majority of these derivatives displayed >1000-fold selectivity over EP4, but a few derivatives such as **7t,** and **7z** displayed only ~600-fold selectivity, and one other compound **7u** displayed a moderate (100-fold) selectivity. Several of these compounds also displayed very good selectivity against the IP receptor. For example **6f** and **9c** displayed ~3000-fold selectivity; **7z,** and **8a** exhibited >1000-fold selectivity; **7j, 7k,** and **7w** exhibited selectivity in the range of 300–600-fold. Furthermore, we tested these derivatives to determine whether they reduced viability of the parent C6-glioma cells, but a majority of these derivatives showed an effect only at high micromolar concentrations (>300 μM) with *in vitro* therapeutic indexes >10,000, except two compounds **7w** and **8a**, both of which showed an effect on cell viability at >100 μM. Nonetheless, *in vitro* therapeutic indexes >6000-fold indicating that the bioactivity by this class of amide compounds is not driven by cell viability (Table 2).

2.5. Second generation amide derivatives show competitive mechanism of inhibition

We have previously demonstrated that first generation acrylamide analogs **1** and **2** exhibit a competitive EP2 antagonism of EP2 [20,23]. To confirm whether the second generation amides derivatives also display competitive antagonism of EP2, we selected 3 potent compounds **6f, 7p, 9a** and subjected them to a concentration–response test on EC_{50} of PGE_2 on EP2 receptors overexpressed in C6-glioma cells. A linear regression of log (dr-1) on log X_B with slope of unity characterizes a competitive antagonism. Schild K_B values are derived by the equation $\log(dr - 1) = \log X_B - \log K_B$, where dr = dose ratio, i.e. the fold shift in EC_{50}; X_B is [antagonist], and K_B is the equilibrium dissociation constant for the antagonist–receptor complex. K_B value indicates the antagonist concentration required for a twofold rightward shift in the PGE_2 dose–response curve. Thus, a lower K_B value indicates a higher inhibitory potency. All the selected members of the second generation compounds induced a concentration-dependent, parallel, rightward shift in the PGE_2 concentration–response curve (Fig. 3A–C). The Schild regression analyses demonstrated that these compounds have a competitive mechanism of antagonism of EP2 (Fig. 3D). Moreover, a less potent carboxylic acid derivative (**7n**), and a 5-tetrazole derivative (**7z**) also displayed competitive antagonism of EP2 with Schild K_B 97 nM for **7n**, and 16.4 nM for **7z** (not shown). Thus, the mechanism is competitive in general in this whole class of second generation EP2 antagonists presented in this study.

2.6. Determination of liver microsomal stability and pharmacokinetics of the second generation amide antagonists

Fifteen potent and selective EP2 antagonists were subjected to a stability test in human and mouse liver microsomal fractions. As shown in Supporting Table 1, several compounds showed moderate to good stability in human microsomes, but a few of them (**6e, 7p, 8z** and **9c**) were metabolized completely in mouse liver microsomes in 60 min (<1% remaining). However, compounds **7j, 7k, 7x,** & **8m** displayed >7% remaining at 60 min in mouse liver fractions, thus are potential candidates to study further. The other noteworthy examples are a 5-tetrazole derivative **7z** and a carboxypiperidine derivative **7n**, both of which displayed high stability in mouse and human liver microsomes with greater than 50% remaining at 60 min. These two derivatives also displayed high aqueous solubility by nephelometry [31], when measured in PBS buffer (pH 7.4) with 1% DMSO (Supporting Table 1).

Although the selectivity of **7z** is moderate against DP1 (30-fold), we selected it for in vivo pharmacokinetic study on the basis of its high stability in both microsomal fractions and its aqueous solubility. As shown in Supporting Table 2, it displayed about 12-fold higher peak concentrations in plasma by intraperitoneal (*ip*) route of administration, in comparison to an oral route (*po*). It

Table 2
EP2 potency, selectivity and cytotoxicity of selected EP2 antagonists.[a]

Entry (Compd. ID)	K_B EP2 nM	K_B EP4 μM	Selective index EP4/EP2	K_B DP1 nM	Selective index (DP1/EP2)	K_B IP μM	Selective index (IP/EP2)	CC_{50} (μM)	Therapeutic index (CC_{50}/EP2 K_B)
6e (TG7-142)	9.8	51	5230	6430	655	4.7	480	310	31,630
6f (TG7-171)	2.7	31.3	11,590	3190	1220	8.0	2960	320	118,520
6g (TG7-192)	11.8	15.5	1320	3550	298	1.12	95	332	28,130
7j (TG7-173)	24.7	28.7	1160	>10,000	>516	14.2	570	337	16,120
7k (TG7-152)	9.4	30.2	3210	2570	273	3.4	360	315	33,510
7o (TG7-185)	22.6	23.6	1045	7720	342	8.5	375	327	14,470
7p (TG7-170)	9.6	21	2190	5210	533	1.98	206	289	30,100
7t (TG7-153)	25.7	14.5	565	2200	85	5.6	217	>500	>19,450
7u (TG7-141)	45	4.76	106	980	22	64.0	1420	300	6660
7w (TG7-180)	26.8	70.3	2620	4620	172	18.1	675	163	6082
7z (TG8-15)	22.3	>10,000	584	660	29	>10,000	1040	>300	>13,450
8a (TG7-178)	20.9	36.1	1730	6290	300	25.2	1200	154	7370
8z (TG7-167)	10.8	16.4	1520	3610	334	63.1	5840	320	29,630
9a (TG7-181)	6.9	48	6945	9480	1374	>10,000	ND	>500	>72,460
9c (TG7-174)	28.6	75.6	2645	7790	272	85.0	2970	311	10,870

[a] EP2, EP4, DP1 and IP K_BS are average of 2–3 independent experiments run in duplicate. CC_{50} are average of one measurement run in triplicate. CC_{50} = critical concentration required to kill 50% cells.

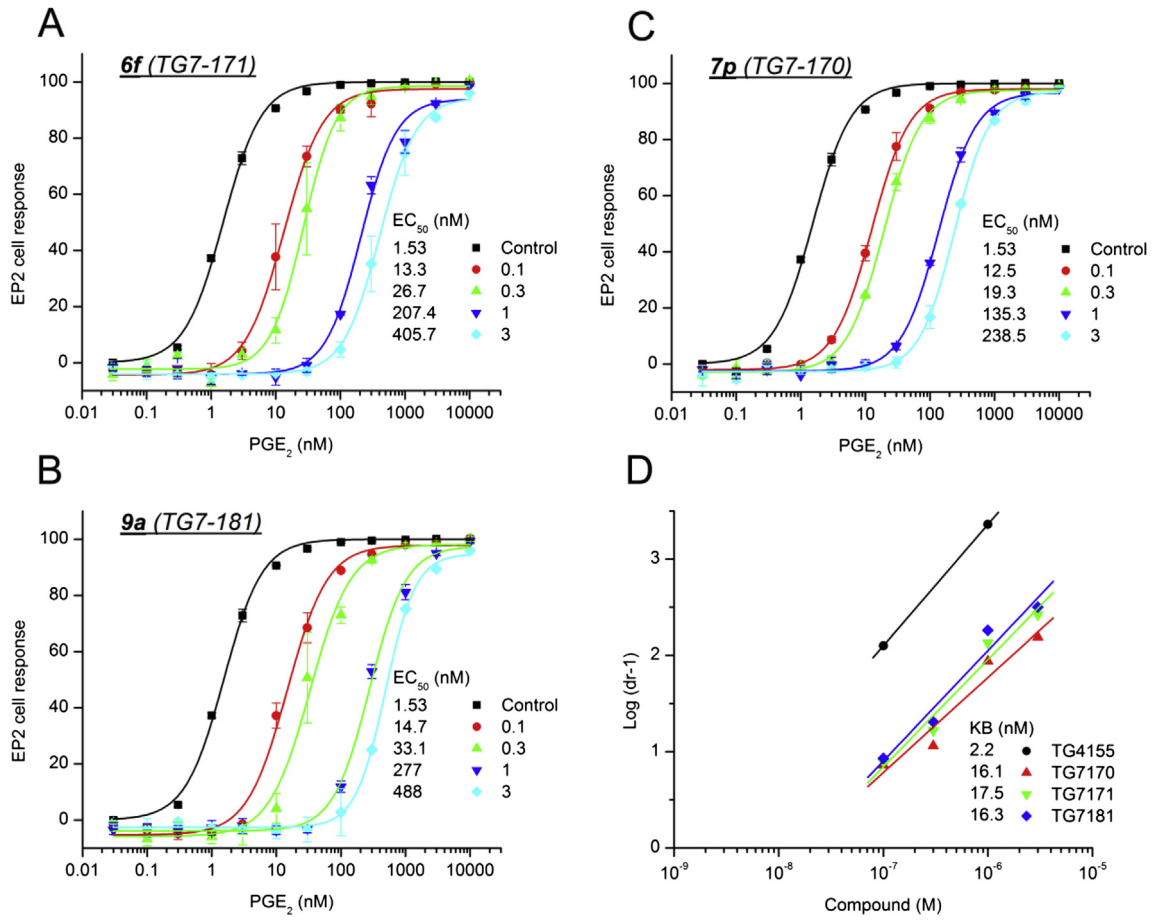


Fig. 3. Competitive antagonism of EP2 receptor by the second generation amide analogs. A–C: Compounds **6f, 7p,** and **9a** inhibits PGE_2-induced human EP2 receptor activation in a concentration dependent manner. D. Schild regression analysis is performed to determine the modality of antagonism by these compounds. K_B values from this experiment, shown in inset of Fig. 2D, are slightly different from the values shown Table 1 which are derived from a single concentration test. However, these are within the limits of assay variation. The Schild plot and the K_B value of compound **1** [20] is shown for comparison.

displayed plasma half-life ($t_{1/2}$) about 0.3 h by *ip* route. We did not calculate $t_{1/2}$ from the oral route due to insufficient data. Moreover, we have not observed any compound in the brain tissue (LLOQ = 10 ng/mL), indicating this compound does not cross the blood brain barrier. Thus, further work is needed to determine whether any other compounds display superior in vivo pharmacokinetics.

2.7. Conclusions

We developed a novel compound series that are devoid of highly vulnerable acrylamide functionality, but still possess high EP2 potency and high selectivity against DP1, EP4 and IP receptors. Further studies to characterize drug-like properties of these selected EP2 antagonists are currently undergoing, but compounds **6e, 6f, 7j, 7p, 8a,** and **9a** display a potent and selective antagonism of the EP2, and may be useful as tools for *in vitro* studies.

3. Experimental

3.1. Chemistry

Proton NMR spectra was recorded on a Varian Inova-400 (400 MHz). Thin layer chromatography was performed on pre-coated, aluminum-backed plates (silica gel 60 F_{254}, 0.25 mm thickness) from EM Science and was visualized by UV lamp. Column chromatography was performed with silica gel cartridges on Teledyne-ISCO machine. Agilent LC–MS was used to measure purity of the products. Elemental analyses were performed by Atlantic Microlab Inc. (Norcross, GA).

3.1.1. *N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-(piperidin-1-yl) benzamide (**7k**) (TG7-152) (typical procedure)*

A solution of 2-(2-methyl-1*H*-indol-1-yl)ethanamine (**4a**) (65 mg, 0.373 mmol) and 4-(piperidin-1-yl)benzoic acid (**5**) (76 mg, 1 eq.), and dimethylaminopyridine (catalytic, ~5 mg) in dichloromethane (6 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide.hydrochloride (EDCI) (92 mg, 1.3 eq.) at room temperature. The resulting reaction mixture was stirred for 6 h. At the conclusion of the reaction (TLC), water (15 mL) was added to quench the reaction. The product was extracted with ethyl acetate (20 mL × 3). Organics were washed with dilute HCl (10 mL), saturated $NaHCO_3$ solution (10 mL), water (10 mL) and brine solution (10 mL) and dried over Na_2SO_4 and concentrated. The resulting crude product was subjected to silica gel chromatography eluting with 0–40% ethyl acetate in hexane to furnish **7k** (TG7-152) (100 mg, 74% yield). ^1H NMR ($CDCl_3$): δ 7.52 (d, J = 5.6 Hz, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8 Hz, 1H), 7.07 (m, 2H), 6.80 (d, J = 8.2 Hz, 2H), 6.23 (s, 1H), 5.98 (t, J = 5.4 Hz, 1H), 4.33 (t, J = 6 Hz, 2H), 3.76 (q, J = 6 Hz, 2H), 3.25 (t, J = 4.8 Hz, 4H), 2.37 (s, 3H), 1.6 (m, 6H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 362 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{27}N_3O$: C, 76.42; H, 7.53; N, 11.62; found; C, 76.48; H, 7.55; N, 11.59.

All other compounds were synthesized analogously by this typical procedure in a 70–80% yield, and then characterized by ^{1}H NMR and LCMS. Representative ^{1}H and ^{13}C NMR spectra for selected compounds are provided in Supporting information. Elemental analysis is recorded for selected compounds (see below).

*3.1.2. 3,4,5-Trimethoxy-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**6a**) (TG7-112-1)*

^{1}H NMR ($CDCl_3$): δ 7.51 (d, J = 7.2 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.07 (m, 2H), 6.74 (s, 2H), 5.98 (t, J = 5.6 Hz, 1H), 4.36 (t, J = 5.6 Hz, 2H), 3.86 (s, 3H), 3.8 (q, J = 5.6 Hz, 2H), 3.77 (s, 6H), 2.41 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 369 $[M+H]^+$.

*3.1.3. 3,4-Dimethoxy-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**6b**) (TG7-112-2)*

^{1}H NMR ($CDCl_3$): δ 7.51 (dd, J = 7.2, 1.6 Hz, 1H), 7.31 (d, J = 6.8 Hz, 1H), 7.23 (d, J = 2 Hz, 1H), 7.0 (m, 3H), 6.77 (d, J = 8.4 Hz, 1H), 6.03 (broad t, 1H), 4.34 (t, J = 6 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.77 (q, J = 6 Hz, 2H), 2.39 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 339 $[M+H]^+$.

*3.1.4. 4-Methoxy-N-(2-(2-methyl-1H-indol-1-yl)ethyl)benzamide (**6c**) (TG7-224)*

^{1}H NMR ($CDCl_3$): δ 7.56 (dd, J = 7.2, 1.2 Hz, 2H), 7.51 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.08 (m, 2H), 6.84 (dd, J = 7.2, 1.2 Hz, 2H), 6.24 (S, 1H), 6.05 (bs, 1H), 4.30 (t, J = 6.4 Hz, 2H), 3.80 (s, 3H), 3.75 (q, J = 6.4 Hz, 2H), 2.37 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 309 $[M+H]^+$.

*3.1.5. 4-(Ethylamino)-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**6d**) (TG7-237)*

^{1}H NMR ($CDCl_3$): δ 7.51 (d, J = 6.8 Hz, 1H), 7.45 (dd, J = 7.2, 1.2 Hz, 2H), 7.31 (d, J = 8.4 Hz, 1H), 7.08 (m, 2H), 6.48 (dd, J = 7.2, 1.2 Hz, 2H), 6.23 (S, 1H), 5.95 (t, 1H), 4.32 (t, J = 6.4 Hz, 2H), 3.75 (q, J = 6 Hz, 2H), 3.16 (q, J = 7.2 Hz, 2H), 2.37 (s, 3H), 1.23 (t, J = 6.8 Hz, 3H), LCMS (ESI): >97% purity at λ 254, MS; m/z, 322 $[M+H]^+$.

*3.1.6. 4-(Dimethylamino)-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**6e**) (TG7-142)*

^{1}H NMR ($CDCl_3$): δ 7.52 (m, 3H), 7.32 (d, J = 7.2 Hz, 1H), 7.08 (m, 2H), 6.63 (d, J = 8.8 Hz, 2H), 6.23 (s, 1H), 5.9 (NH, 1H), 4.33 (t, J = 5.6 Hz, 2H), 3.76 (q, J = 6 Hz, 2H), 2.99 (s, 6H), 2.37 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 395 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{23}N_3O$; C, 74.74; H, 7.21; N, 13.07; Found; C, 74.37; H, 7.16; N, 12.83.

*3.1.7. 4-(Diethylamino)-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**6f**) (TG7-171)*

^{1}H NMR ($CDCl_3$): δ 7.49 (m, 3H), 7.32 (d, J = 8 Hz, 1H), 7.08 (m, 2H), 6.56 (d, J = 9.2 Hz, 2H), 6.23 (s, 1H), 5.95 (t, J = 6 Hz, 1H), 4.32 (t, J = 5.6 Hz, 2H), 3.76 (q, J = 6 Hz, 2H), 3.37 (q, J = 7.2 Hz, 4H), 2.37 (s, 3H), 1.15 (t, J = 7.2 Hz, 6H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 350 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{23}N_3O$; C, 75.61; H, 7.79; N, 12.02; Found; C, 75.47; H, 7.74; N, 11.86.

*3.1.8. 4-(Dipropylamino)-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**6g**) (TG7-192)*

^{1}H NMR ($CDCl_3$): δ 7.51 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 6.8 Hz, 2H), 7.32 (d, J = 7.2 Hz, 1H), 7.09 (m, 2H), 6.52 (d, J = 8.8 Hz, 2H), 6.23 (s, 1H), 5.92 (t, J = 6 Hz, 1H), 4.32 (t, J = 6 Hz, 2H), 3.76 (t, J = 6 Hz, 2H), 3.24 (t, J = 7.6 Hz, 4H), 2.37 (s, 3H), 1.60 (q, J = 7.6 Hz, 4H), 0.91 (t, J = 7.2 Hz, 6H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 378 $[M+H]^+$. Anal. Calcd. for $C_{24}H_{31}N_3O$; C, 76.35; H, 8.28; N, 11.13; found, C, 76.08; H, 8.12; N, 10.97.

*3.1.9. 4-(Dibutylamino)-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**6h**) (TG7-188)*

^{1}H NMR ($CDCl_3$): δ 7.51 (d, J = 7.6 Hz, 1H), 7.47 (dd, J = 9.2 Hz, 2H), 7.32 (d, J = 8 Hz, 1H), 7.08 (m, 2H), 6.52 (d, J = 8.8 Hz, 2H), 6.23 (s, 1H), 5.93 (t, J = 5.6 Hz, 1H), 4.32 (t, J = 6 Hz, 2H), 3.75 (t, J = 6 Hz, 2H), 3.26 (t, J = 8 Hz, 4H), 2.37 (s, 3H), 1.54 (m, 4H), 1.32 (m, 4H), 0.93 (t, J = 7.2 Hz, 6H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 406 $[M+H]^+$.

*3.1.10. 4-Amino-N-(2-(2-methyl-1H-indol-1-yl)ethyl)benzamide (**6i**)(TG7-143)*

^{1}H NMR ($CDCl_3$): δ 7.46 (d, J = 7.2 Hz, 1H), 7.40 (dd, J = 6.8, 2 Hz, 2H), 7.26 (d, J = 8 Hz, 1H),7.03 (m, 2H), 6.58 (dd, J = 6.8, 2 Hz, 2H), 4.27 (t, J = 6 Hz, 2H), 3.66 (t, J = 5.6 Hz, 2H), 2.3 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 294 $[M+H]^+$.

*3.1.11. 4-Hydroxy-N-(2-(2-methyl-1H-indol-1-yl)ethyl)benzamide (**6j**) (TG7-223)*

^{1}H NMR ($CDCl_3$): δ 7.50 (m, 3H), 7.29 (d, J = 8 Hz, 1H), 7.08 (m, 2H), 6.78 (m, 2H), 6.24 (s, 1H), 6.04 (t, J = 6 Hz, 1H), 4.33 (t, J = 6.2 Hz, 2H), 3.77 (q, J = 6.2 Hz, 2H), 2.37 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 295 $[M+H]^+$.

*3.1.12. 4-Guanidino-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**6k**) (TG7-179)*

^{1}H NMR ($CDCl_3$): δ 7.48 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 2H), 6.99 (m, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.17 (s, NH), 4.25 (t, J = 6.4 Hz, 2H), 3.6 (q, J = 6 Hz, 2H), 2.32 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 336 $[M+H]^+$.

*3.1.13. N-(2-(1H-Indol-1-yl)ethyl)-4-(diethylamino)benzamide (**6l**) (TG7-205)*

^{1}H NMR ($CDCl_3$): δ 7.63 (d, J = 8 Hz, 1H), 7.49 (dd, J = 7, 1.6 Hz, 2H), 7.40 (d, J = 8 Hz, 1H), 7.19 (t, J = 7.8 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 3.2 Hz, 1H), 6.56 (d, J = 9.2 Hz, 2H), 6.4 (d, J = 2.8 Hz, 1H), 5.89 (t, J = 5.4 Hz, 1H), 4.35 (t, J = 5.6 Hz, 2H), 3.79 (q, J = 6 Hz, 2H), 3.71 (q, J = 7.2 Hz, 4H), 1.15 (t, J = 6.8 Hz, 6H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 351 $[M+H]^+$.

*3.1.14. 4-((2-(2-methyl-1H-indol-1-yl)ethyl)carbamoyl)phenyl acetate (**6m**) (TG7-233)*

^{1}H NMR ($CDCl_3$): δ 7.60 (d, J = 7.2 Hz, 2H), 7.51 (d, J = 8 Hz, 1H), 7.30 (d, J = 8 Hz, 1H), 7.08 (m, 4H), 6.25 (s, 1H), 6.08 (broad triplet, 1H), 4.34 (t, J = 6 Hz, 2H), 3.77 (q, J = 6 Hz, 2H), 2.38 (s, 3H), 2.28 (s, 3H). LCMS (ESI): >98% purity at λ 254, MS; m/z, 295 $[M+H]^+$.

*3.1.15. 4-Acetamido-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**6n**) (TG7-117)*

^{1}H NMR (DMSO-d_6): δ 7.49 (m, 5H), 7.25 (dd, J = 7.2 Hz, 1H), 6.98 (m, 2H), 4.23 (t, J = 6.4 Hz, 2H), 3.61 (t, J = 6.4 Hz, 2H), 2.29 (s, 3H), 2.0 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 336 $[M+H]^+$.

*3.1.16. 3-Fluoro-4-(2-fluorobenzamido)-N-(2-(2-methyl-1H-indol-1-yl)ethyl)benzamide (**6o**) (TG7-157)*

^{1}H NMR ($CDCl_3$): δ 8.90 (d, J = 16.8 Hz, 2H), 8.49 (t × d, J = 6.8, 3.2 Hz, 1H), 8.11 (t, J = 7.6 Hz, 1H), 7.52 (m, 3H), 7.30 (m, 3H), 7.17 (m, 1H), 7.08 (m, 2H), 4.34 (t, J = 6.2 Hz, 2H), 3.72 (q, J = 6.2 Hz, 2H), 2.35 (s, 3H). LCMS (ESI): >98% purity at λ 254, MS; m/z, 434 $[M+H]^+$.

*3.1.17. N-(2-(2-methyl-1H-indol-1-yl)ethyl)terephthalamide (**6p**) (TG7-140)*

^{1}H NMR ($CDCl_3$): δ 7.75 (dd, J = 7.2, 1.8 Hz, 2H), 7.62 (dd, J = 7.6, 1.6 Hz, 2H), 7.45 (m, 1H), 7.25 (m, 1H), 7.0 (m, 2H), 4.3 (m, 2H), 3.6 (m, 2H), 2.33 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 322 $[M+H]^+$.

*3.1.18. N, N-dimethyl-N4-(2-(2-methyl-1H-indol-1-yl)ethyl) terephthalamide (**6q**) (TG7-227)*

^{1}H NMR ($CDCl_3$): δ 7.58 (dd, J = 7.2, 2 Hz, 1H), 7.51 (d, J = 8 Hz, 1H), 7.34 (d, J = 7.2 Hz, 2H), 7.30 (d, J = 8 Hz, 1H), 7.07 (m, 2H), 6.36 (broad triplet, 1H), 6.25 (s, 1H), 4.36 (t, J = 6 Hz, 2H), 3.78 (q, J = 6 Hz, 2H), 3.05 (s, 3H), 2.89 (s, 3H), 2.38 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 350 $[M+H]^+$.

*3.1.19. N, N-diethyl-N4-(2-(2-methyl-1H-indol-1-yl)ethyl) terephthalamide (**6r**) (TG7-226)*

^{1}H NMR ($CDCl_3$): δ 7.55 (d, J = 7.6 Hz, 2H), 7.49 (d, J = 8 Hz, 1H), 7.31 (d, J = 8 Hz, 1H), 7.20 (m, 2H), 7.06 (m, 2H), 6.85 (broad singlet, 1H), 4.33 (t, J = 6 Hz, 2H), 3.73 (q, J = 5.6 Hz, 2H), 3.40 (broad singlet, 2H), 3.13 (broad singlet, 2H), 2.39 (s, 3H), 1.19 (broad singlet, 3H), 1.03 (broad singlet, 3H). Note: The *N*-ethyl groups did not show usual spitting pattern of quartet and triplet. LCMS (ESI): >95% purity at λ 254, MS; m/z, 377 $[M+H]^+$.

*3.1.20. 4-Cyano-N-(2-(2-methyl-1H-indol-1-yl)ethyl)benzamide (**6s**) (TG7-147)*

^{1}H NMR ($CDCl_3$): δ 7.64 (m, 4H), 7.51 (m, 1H), 7.27 (m, 1H), 7.06 (m, 2H), 6.1 (t, J = 5 Hz, NH), 4.37 (t, J = 6 Hz, 2H), 3.81 (q, J = 6 Hz, 2H), 2.38 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 304 $[M+H]^+$.

*3.1.21. ^{t}Butyl 4-((2-(2-methyl-1H-indol-1-yl)ethyl)-carbamoyl) benzoate (**6t**) (TG7-172)*

^{1}H NMR ($CDCl_3$): δ 7.95 (dd, J = 6.8 Hz, 2H), 7.59 (dd, J = 6.8, 2 Hz, 2H), 7.51 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.08 (m, 2H), 6.25 (s, 1H), 6.15 (t, J = 5.4 Hz, 1H), 4.36 (t, J = 5.6 Hz, 2H), 3.8 (q, J = 6 Hz, 2H), 2.37 (s, 3H), 1.57 (s, 9H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 379 $[M+H]^+$.

*3.1.22. 4-((2-(2-Methyl-1H-indol-1-yl)ethyl)carbamoyl)benzoic acid (**6u**) (TG7-176)*

^{1}H NMR ($CDCl_3$): δ 8.0 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8 Hz, 2H), 7.48 (dd, J = 6.6, 1.6 Hz, 1H), 7.27 (d, J = 8 Hz, 1H), 7.0 (m, 2H), 6.88 (t, J = 6 Hz, 1H), 6.2 (s, 1H), 4.32 (t, J = 5.8 Hz, 2H), 3.74 (q, J = 5.6 Hz, 2H), 2.34 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 323 $[M+H]^+$.

*3.1.23. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-sulfamoylbenzamide (**6v**) (TG7-161)*

^{1}H NMR (DMSO-d_6): δ 8.84 (t, J = 5.6 Hz, 1H), 7.87 (q, J = 8.8 Hz, 4H), 7.44 (s, 2H), 7.38 (t, J = 8 Hz, 2H), 7.0 (t, J = 7.6 Hz, 1H), 6.92 (t, J = 7.6 Hz, 1H), 6.16 (s, 1H), 4.26 (t, J = 6.4 Hz, 2H), 3.53 (q, J = 6.4 Hz, 2H), 2.35 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 358 $[M+H]^+$.

*3.1.24. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-3-sulfamoylbenzamide (**6w**) (TG7-165)*

^{1}H NMR (DMSO-d_6): δ 8.9 (t, J = 5.6 Hz, 1H), 8.27 (t, J = 2 Hz, 1H), 7.93 (dd, J = 8, 1.6 Hz, 2H), 7.63 (t, J = 7.6 Hz, 1H), 7.43 (s, 2H), 7.39 (t, J = 8.4 Hz, 2H), 7.01 (t × d, J = 7.4, 1.2 Hz, 1H), 6.92 (t, J = 7.2 Hz, 1H), 6.16 (s, 1H), 4.26 (t, J = 6.4 Hz, 2H), 3.53 (q, J = 6 Hz, 2H), 2.35 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 358 $[M+H]^+$.

*3.1.25. ^{t}Butyl (4-((2-(2-methyl-1H-indol-1-yl)ethyl)carbamoyl) benzyl)carbamate (**6x**) (TG7-254)*

^{1}H NMR ($CDCl_3$): δ 7.52 (d, J = 7.2 Hz, 2H), 7.44 (d, J = 8 Hz, 1H), 7.25 (m, 4H), 7.02 (m, 2H), 4.28 (t, J = 6 Hz, 2H), 4.23 (s, 2H), 3.67 (t, J = 6 Hz, 2H), 2.31 (s, 3H), 1.37 (s, 9H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 408 $[M+H]^+$.

*3.1.26. 4-(Aminomethyl)-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**6y**) (TG7-258)*

^{1}H NMR ($CDCl_3$): δ 7.55 (d, J = 7.2 Hz, 2H), 7.50 (d, J = 8 Hz, 2H), 7.28 (m, 3H), 7.06 (m, 2H), 6.30 (broad triplet, 1H), 6.22 (s, 1H), 4.39 (s, 2H), 4.31 (t, J = 6 Hz, 2H), 3.73 (q, J = 6.2 Hz, 2H), 2.35 (s, 3H). LCMS (ESI): >90% purity at λ 254, MS; m/z, 308 $[M+H]^+$.

*3.1.27. 4-(2-Aminoethyl)-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**6z**) (TG7-272)*

^{1}H NMR ($CDCl_3$): δ 7.51 (t, J = 7.6 Hz, 3H), 7.30 (d, J = 8 Hz, 1H), 7.15 (d, J = 8 Hz, 1H), 7.07 (m, 2H), 6.40 (broad triplet, 1H), 6.23 (s, 1H), 4.32 (t, J = 6 Hz, 2H), 3.74 (q, J = 6 Hz, 2H), 2.89 (q, J = 6.8 Hz, 2H), 2.71 (q, J = 6.8 Hz, 2H), 2.36 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 322 $[M+H]^+$.

*3.1.28. 4-(Dimethylamino)-3-fluoro-N-(2-(2-methyl-1H-indol-1-yl)ethyl)benzamide (**7a**)(TG7-164)*

^{1}H NMR ($CDCl_3$): δ 7.51 (d, J = 7.6 Hz, 1H), 7.32 (dd, J = 11, 2.4 Hz, 1H), 7.29 (s, 1H), 7.21 (dd, J = 8.4, 2 Hz, 1H), 7.09 (m, 2H), 6.72 (t, J = 8.8 Hz, 1H), 6.24 (s, 1H), 5.96 (t, J = 6 Hz, 1H), 4.33 (t, J = 6 Hz, 2H), 3.75 (q, J = 6 Hz, 2H), 2.91 (s, 6H), 2.37 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 340 $[M+H]^+$.

*3.1.29. 4-Acetamido-3-fluoro-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**7b**) (TG7-158)*

^{1}H NMR (DMSO-d_6): δ 9.98 (s, 1H), 8.85 (t, J = 5.6 Hz, 1H), 8.0 (t, J = 8 Hz, 1H), 7.58 (m, 2H), 7.38 (t, J = 6.4 Hz, 2H), 7.0 (t, J = 7.6 Hz, 1H), 6.92 (t, J = 7.6 Hz, 1H), 6.20 (s, 1H), 4.23 (t, J = 6.8 Hz, 2H), 3.49 (q, J = 6.8 Hz, 2H), 2.34 (s, 3H), 2.08 (s, 3H). LCMS (ESI): >98% purity at λ 254, MS; m/z, 354 $[M+H]^+$.

*3.1.30. 3-Fluoro-4-methoxy-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**7c**) (TG7-225)*

^{1}H NMR ($CDCl_3$): δ 7.52 (d, J = 6.8 Hz, 1H), 7.38 (dd, J = 11.6, 2 Hz, 1H), 7.28 (m, 2H), 7.08 (m, 2H), 6.89 (t, J = 8.4 Hz, 1H), 6.25 (s, 1H), 5.98 (broad singlet, 1H), 4.34 (t, J = 6.2 Hz, 2H), 3.89 (s, 3H), 3.77 (q, J = 6.2 Hz, 2H), 2.37 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 327 $[M+H]^+$.

*3.1.31. 4-(Diethylamino)-3-fluoro-N-(2-(2-methyl-1H-indol-1-yl) ethyl)benzamide (**7d**) (TG7-206)*

^{1}H NMR ($CDCl_3$): δ 7.51 (d, J = 7.2 Hz, 2H), 7.32–7.27 (m, 2H), 7.19 (dd, J = 8.4, 2.4 Hz, 1H), 7.13–7.04 (m, 2H), 6.71 (t, J = 8.8 Hz, 1H), 6.21 (s, 1H), 5.98 (t, J = 5.4 Hz, 1H), 4.33 (t, J = 6 Hz, 2H), 3.75 (q, J = 5.6 Hz, 2H), 3.3 (q, J = 6.8 Hz, 4H), 2.3 (s, 3H), 1.26 (t, J = 6.8 Hz, 6H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 368 $[M+H]^+$.

*3.1.32. 4-(Diethylamino)-N-(2-(2-methyl-1H-indol-1-yl)ethyl)-3-(trifluoromethyl)benzamide (**7e**) (TG7-213)*

^{1}H NMR ($CDCl_3$): δ 7.86 (d, J = 2 Hz, 1H), 7.68 (dd, J = 8.4, 2 Hz, 1H), 7.52 (dd, J = 7, 1.6 Hz, 1H), 7.30 (d, J = 8 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.08 (m, 2H), 6.26 (t, J = 1.2 Hz, 1H), 6.06 (d, J = 5.4 Hz, 1H), 4.35 (t, J = 5.6 Hz, 2H), 3.79 (q, J = 6.4 Hz, 2H), 3.0 (q, J = 7.2 Hz, 4H), 2.4 (s, 3H), 0.98 (t, J = 7.2 Hz, 6H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 418 $[M+H]^+$.

*3.1.33. 4-(Ethylamino)-N-(2-(2-methyl-1H-indol-1-yl)ethyl)-3-(trifluoromethyl)benzamide (**7f**) (TG6-201)*

^{1}H NMR ($CDCl_3$): δ 7.45 (d, J = 2 Hz, 1H), 7.59 (dd, J = 8.6, 2.4 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.07 (m, 2H), 6.63 (d, J = 8.8 Hz, 1H), 6.2 (s, 1H), 5.96 (t, J = 5.6 Hz, 1H), 4.55 (bs, 1H), 4.33 (t, J = 6 Hz, 2H), 3.76 (q, J = 6 Hz, 2H), 3.2 (m, 2H), 2.3 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 390 $[M+H]^+$.

*3.1.34. 4-(Diethylamino)-3-methoxy-N-(2-(2-methyl-1H-indol-1-yl)ethyl)benzamide (**7g**) (TG7-214)*

^{1}H NMR ($CDCl_3$): δ 7.51 (d, J = 7.6 Hz, 1H), 7.33 (dd, J = 8 Hz, 1H), 7.21 (d, J = 2 Hz, 1H), 7.09 (m, 2H), 7.0 (dd, J = 8.4, 2 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.25 (s, 1H), 6.05 (t, J = 5.2 Hz, 1H), 4.34 (t, J = 5.6 Hz, 2H), 3.82 (s, 3H), 3.78 (t, J = 6.4 Hz, 2H), 3.21 (q, J = 7.2 Hz, 2H), 2.40 (s, 3H), 1.03 (t, J = 6.8 Hz, 6H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 380 $[M+H]^+$.

*3.1.35. 4-Cyano-3-fluoro-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**7h**) (TG7-155-1)*

^{1}H NMR ($CDCl_3$): δ 7.60 (dd, J = 8, 6.4 Hz, 1H), 7.52 (dd, J = 6.2, 3.6 Hz, 1H), 7.40 (dd, J = 9.2, 1.6 Hz, 1H), 7.29 (dd, J = 8.2, 1.6 Hz, 1H), 7.25 (m, 2H), 7.07 (m, 2H), 6.07 (t, J = 5.4 Hz, 1H), 4.36 (t, J = 6 Hz, 2H), 3.8 (t, J = 6 Hz, 2H), 2.39 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 322 $[M+H]^+$.

*3.1.36. 4-Cyano-2-fluoro-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**7i**)(TG7-155-2)*

^{1}H NMR ($CDCl_3$): δ 8.5 (t, J = 8 Hz, 1H), 7.55 (dd, J = 8.2,1.6 Hz, 1H), 7.5 (dd, J = 7.4, 1.6 Hz, 1H), 7.38 (dd, J = 10, 1.6 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.06 (m, 1H), 6.67 (m, 1H), 6.24 (s, 1H), 4.36 (t, J = 6 Hz, 2H), 3.80 (q, J = 6 Hz, 2H), 2.4 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 322 $[M+H]^+$.

*3.1.37. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-(pyrrolidin-1-yl) benzamide (**7j**) (TG7-173)*

^{1}H NMR ($CDCl_3$): δ 7.50 (dd, J = 6.8, 2 Hz, 3H), 7.32 (d, J = 8.4 Hz, 1H), 7.0 (m, 2H), 6.45 (d, J = 8.4 Hz, 2H), 6.23 (s, 1H), 5.96 (t, J = 6 Hz, 1H), 4.33 (t, J = 6 Hz, 2H), 3.75 (q, J = 6 Hz, 2H), 3. 29 (t, J = 6.4 Hz, 4H), 2.37 (s, 3H), 2.0 (m, 4H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 348 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{25}N_3O$; C, 76.05; H, 7.25; N, 12.09; found; C, 75.98; H, 7.25; N, 11.95.

3.1.38. 7k (TG7-152)

Please see Section 3.1.1.

*3.1.39. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-(4-methylpiperidin-1-yl)benzamide (**7l**) (TG7-240)*

^{1}H NMR ($CDCl_3$): δ 7.52 (d, J = 6.8 Hz, 3H), 7.32 (d, J = 6.8 Hz, 1H), 7.07 (m, 2H), 6.80 (d, J = 6 Hz, 2H), 6.23 (s, 1H), 6.0 (t, J = 5 Hz, 1H), 4.32 (t, J = 6 Hz, 2H), 3.75 (q, J = 6.8 Hz, 2H), 2. 80 (t, J = 6.8 Hz, 2H), 2.37 (s, 3H), 1.73 (broad doublet, J = 8.4 Hz, 2H), 1.60 (m, 1H), 1.45 (m, 3H), 1.20 (m, 2H), 0.99 (d, J = 6.4 Hz, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 376 $[M+H]^+$.

*3.1.40. Ethyl-1-(4-((2-(2-methyl-1H-indol-1-yl)ethyl)carbamoyl) phenyl)piperidine-4-carboxylate (**7m**) (TG8-24)*

^{1}H NMR ($CDCl_3$): δ 7.52 (m, 3H), 7.31 (d, J = 8 Hz, 1H), 7.08 (m, 2H), 6.81 (d, J = 6 Hz, 2H), 6.23 (s, 1H), 5.97 (t, J = 4 Hz, 1H), 4.33 (t, J = 6 Hz, 2H), 4.1 (q, J = 7.2 Hz, 2H), 3.76 (q, J = 6 Hz, 2H), 3. 72 (q, J = 3.6 Hz, 2H), 2.88 (m, 2H), 2.46 (m, 1H), 2.37 (s, 3H), 2.01 (m, 2H), 1.81 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 434 $[M+H]^+$.

*3.1.41. 1-(4-((2-(2-Methyl-1H-indol-1-yl)ethyl)carbamoyl)phenyl) piperidine-4-carboxylic acid (**7n**) (TG8-29)*

^{1}H NMR ($CDCl_3$): δ 7.52 (m, 3H), 7.31 (d, J = 8 Hz, 1H), 7.08 (m, 2H), 6.81 (d, J = 6 Hz, 2H), 6.24 (s, 1H), 5.98 (t, J = 5.6 Hz, 1H), 4.33 (t, J = 6 Hz, 2H), 3.77 (m, 4H), 2.98 (m, 2H), 2.5 (m, 1H), 2.37 (s, 3H), 2.02 (m, 2H), 1.84 (m, 2H). LCMS (ESI): >98% purity at λ 254, MS; m/z, 406 $[M+H]^+$.

*3.1.42. 4-(Azepan-1-yl)-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**7o**) (TG7-185)*

^{1}H NMR ($CDCl_3$): δ 7.50 (m, 3H), 7.33 (d, J = 8 Hz, 1H), 7.08 (m, 2H), 6.58 (d, J = 6.8 Hz, 2H), 6.23 (s, 1H), 5.95 (t, J = 6.4 Hz, 1H), 4.32 (t, J = 6 Hz, 2H), 3.75 (q, J = 6 Hz, 2H), 3. 45 (t, J = 6 Hz, 4H), 2.38 (s, 3H), 1.76 (m, 4H), 1.51 (m, 4H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 376 $[M+H]^+$. Anal. Calcd. for $C_{24}H_{29}N_3O$; C, 76.76; H, 7.78; N, 11.19; found; C, 75.84; H, 7.65; N, 10.91.

*3.1.43. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-morpholinobenzamide (**7p**) (TG7-170)*

^{1}H NMR ($CDCl_3$): δ 7.52 (m, 3H), 7.31 (d, J = 8 Hz, 1H), 7.09 (m, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.24 (s, 1H), 5.99 (t, J = 6.4 Hz, 1H), 4.34 (t, J = 5.6 Hz, 2H), 3.83 (t, J = 4.8 Hz, 4H), 3.77 (q, J = 5.6 Hz, 2H), 3. 21 (t, J = 5.2 Hz, 4H), 2.37 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 364 $[M+H]^+$. Anal. Calcd for $C_{22}H_{25}N_3O_2$; C, 72.70; H, 6.93; N, 11.56; found, C, 72.49; H, 6.91; N, 11.39.

*3.1.44. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-(4-methylpiperazin-1-yl)benzamide (**7q**) (TG7-166)*

^{1}H NMR ($CDCl_3$): δ 7.50 (m, 2H), 7.29 (d, J = 8 Hz, 1H), 7.07 (m, 2H), 6.78 (d, J = 8.8 Hz, 2H), 6.22 (s, 2H), 4.29 (t, J = 5.6 Hz, 2H), 3.70 (q, J = 6 Hz, 2H), 3.25 (t, J = 4.8 Hz, 4H), 2.51 (t, J = 5.2 Hz, 4H) 2.35 (s, 3H), 2.31 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 377 $[M+H]^+$.

*3.1.45. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-3-(4-methylpiperazin-1-yl)benzamide (**7r**)(TG7-255)*

^{1}H NMR ($CDCl_3$): δ 7.50 (d, J = 7.2 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.20–6.95 (m, 6H), 6.25 (s, 1H), 6.10 (broad triplet, 1H), 4.34 (t, J = 6 Hz, 2H), 3.76 (q, J = 6 Hz, 2H), 3.23 (t, J = 5.2 Hz, 4H), 2.63 (broad singlet, 4H), 2.40 (s, 3H), 2.39 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 377 $[M+H]^+$.

*3.1.46. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-3-morpholinobenzamide (**7s**) (TG7-256)*

^{1}H NMR ($CDCl_3$): δ 7.50 (d, J = 7 Hz, 1H), 7.31 (d, J = 7 Hz, 1H), 7.27 (m, 2H), 7.18 (m, 4H), 6.25 (s, 1H), 6.18 (broad triplet), 4.35 (t, J = 6 Hz, 2H), 3.89 (t, J = 5.2 Hz, 4H), 3.78 (q, J = 6 Hz, 2H), 3. 16 (t, J = 4.8 Hz, 4H), 2.40 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 364 $[M+H]^+$.

*3.1.47. 3-Fluoro-N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-morpholinobenzamide (**7t**) (TG7-153)*

^{1}H NMR ($CDCl_3$): δ 7.52 (d, J = 7.8 Hz, 1H), 7.34 (dd, J = 10.2, 2.4 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.22 (m, 1H), 7.08 (m, 2H), 6.83 (t, J = 8.4 Hz, 1H), 6.25 (s, 1H), 6.0 (t, J = 5 Hz, 1H), 4.33 (t, J = 5.6 Hz, 2H), 3.84 (t, J = 4.4 Hz, 4H), 3.76 (q, J = 6 Hz, 2H), 3. 13 (q, J = 4 Hz, 4H), 2.37 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 381 $[M + H]^+$. Anal. Calcd. for $C_{22}H_{24}FN_3O_2$; C, 69.27; H, 6.34; N, 11.02; found; C, 69.10; H, 6.48; N, 11.00.

*3.1.48. 3-Fluoro-N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-(4-methylpiperazin-1-yl)benzamide (**7u**) (TG7-141)*

^{1}H NMR ($CDCl_3$): δ 7.49 (dd, J = 7.2, 1.2 Hz, 1H), 7.33 (m, 3H), 7.07 (m, 2H), 6.81 (t, J = 8.4 Hz, 1H), 6.24 (m, 1H), 6.23 (s, 1H), 4.29 (t, J = 5.6 Hz, 2H), 3.70 (q, J = 6.4 Hz, 2H), 3.15 (broad t, J = 4.4 Hz, 4H), 2.55 (t, J = 4.8 Hz, 4H) 2.35 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 395 $[M+H]^+$.

*3.1.49. 4-(4-Methyl-1,4-diazepan-1-yl)-N-(2-(2-methyl-1H-indol-1-yl)ethyl)benzamide (**7v**) (TG7-182)*

^{1}H NMR ($CDCl_3$): δ 7.50 (m, 1H), 7.48 (d, J = 7.2 Hz, 2H), 7.31 (d, J = 7.6 Hz, 1H), 7.08 (m, 2H), 6.57 (d, J = 9.2 Hz, 2H), 6.22 (s, 1H), 6.13 (t, J = 6 Hz, 1H), 4.29 (t, J = 6.4 Hz, 2H), 3.71 (q, J = 6 Hz, 2H), 3.55 (t,

J = 4.8 Hz, 2H), 3.47 (t, J = 6.4 Hz, 2H), 2.65 (t, J = 4.8 Hz, 2H) 2.51 (t, J = 5.6 Hz, 2H), 2.36 (s, 3H), 2.34 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 391 $[M+H]^+$.

*3.1.50. 4-(4-Hydroxypiperidin-1-yl)-N-(2-(2-methyl-1H-indol-1-yl)ethyl)benzamide (**7w**) (TG7-180)*

^{1}H NMR ($CDCl_3$): δ 7.52 (m, 1H), 7.50 (dd, J = 7.2, 2 Hz, 2H), 7.31 (d, J = 8 Hz, 1H), 7.07 (m, 2H), 6.81 (dd, J = 8.2, 2.8 Hz, 2H), 6.23 (s, 1H), 6.04 (t, J = 6 Hz, 1H), 4.32 (t, J = 6 Hz, 2H), 3.85 (m, 1H), 3.73 (q, J = 6 Hz, 2H), 3.64 (m, 2H), 3.01 (m, 2H), 2.36 (s, 3H), 1.92 (m, 2H), 1.59 (m, 2H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 378 $[M+H]^+$.

*3.1.51. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-(1H-tetrazol-1-yl) benzamide (**7x**) (TG7-159)*

^{1}H NMR (DMSO-d_6): δ 10.1 (s, 1H), 8.8 (t, J = 5.6 Hz, 1H), 8.0 (s, 4H), 7.40 (dd, J = 9.6, 8 Hz, 2H), 7.0 (t, J = 7.4 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 6.1 (s, 1H), 4.28 (t, J = 6.8 Hz, 2H), 3.5 (q, J = 6.8 Hz, 2H), 2.36 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 358 $[M+H]^+$.

*3.1.52. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-(5-thioxo-4,5-dihydro-1H-tetrazol-1-yl)benzamide (**7y**) (TG8-8)*

^{1}H NMR (DMSO-d_6): δ 8.74 (t, J = 5.4 Hz, 1H), 8.20 (dd, J = 7, 2 Hz, 2H), 7.84 (d, J = 7.2, 2 Hz, 2H), 7.40 (dd, J = 15.4, 7.6 Hz, 1H), 7.02 (t, J = 8 Hz, 1H), 6.94 (t, J = 8 Hz, 1H), 6.16 (s, 1H), 4.26 (t, J = 6.4 Hz, 2H), 3.52 (q, J = 6.4 Hz, 2H), 2.37 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 379 $[M+H]^+$.

*3.1.53. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-(5-thioxo-4,5-dihydro-1H-tetrazol-1-yl)benzamide (**7z**) (TG8-15)*

^{1}H NMR (DMSO-d_6): δ 8.83 (t, J = 5.6 Hz, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 7.39 (dd, J = 15.4, 7.6 Hz, 1H), 7.01 (t, J = 8 Hz, 1H), 6.94 (t, J = 8 Hz, 1H), 6.16 (s, 1H), 4.27 (t, J = 6.4 Hz, 2H), 3.52 (q, J = 6.4 Hz, 2H), 2.36 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 347 $[M+H]^+$.

*3.1.54. 1,3-Dimethyl-N-(2-(2-methyl-1H-indol-1-yl)ethyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxamide (**8a**) (TG7-178)*

^{1}H NMR ($CDCl_3$): δ 7.53 (dd, J = 6.4, 1.6 Hz, 1H), 7.32 (d, J = 8 Hz, 1H), 7.27 (s, 1H), 7.25 (m, 1H), 7.0 (m, 2H), 6.88 (d, J = 8 Hz, 1H), 6.28 (s, 1H), 6.10 (t, J = 5.6 Hz, 1H), 4.37 (t, J = 6 Hz, 2H), 3.8 (q, J = 5.6 Hz, 2H), 3.40 (s, 3H), 2.39 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 363 $[M+H]^+$. Anal. Calcd. for $C_{21}H_{22}N_4O_2$; C, 69.59; H, 6.12; N, 15.46; found; C, 69.45; H, 6.14; N, 15.36.

*3.1.55. 4-Cyclohexyl-N-(2-(2-methyl-1H-indol-1-yl)ethyl) benzamide (**8b**) (TG7-193)*

^{1}H NMR ($CDCl_3$): δ 7.50 (d, J = 7.6 Hz, 3H), 7.31 (d, J = 8 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.08 (m, 2H), 6.25 (s, 1H), 6.07 (t, J = 6 Hz, 1H), 4.34 (t, J = 6 Hz, 2H), 3.78 (q, J = 6 Hz, 2H), 2.5 (m, 1H), 2.38 (s, 3H), 1.83 (m, 4H), 1.73 (m, 2H), 1.37 (m, 4H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 361 $[M+H]^+$.

*3.1.56. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-(piperazin-1-yl) benzamide (**8c**) (TG7-202-2)*

^{1}H NMR ($CDCl_3$): δ 7.51 (d, J = 9.2 Hz, 2H), 7.31 (d, J = 8 Hz, 1H), 7.08 (m, 2H), 6.81 (d, J = 8.8 Hz, 1H), 6.23 (s, 1H), 6.18 (t, J = 5.4 Hz, 1H), 4.33 (t, J = 6 Hz, 2H), 3.77 (q, J = 6 Hz, 2H), 3.21 (q, J = 4.8 Hz, 4H), 2.99 (t, J = 4.8 Hz, 4H), 2.37 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 363 $[M+H]^+$.

*3.1.57. 4-(4-Acetylpiperazin-1-yl)-N-(2-(2-methyl-1H-indol-1-yl) ethyl)benzamide (**8d**) (TG7-211)*

^{1}H NMR ($CDCl_3$): δ 7.52 (m, 3H), 7.31 (d, J = 8 Hz, 1H), 7.08 (m, 2H), 6.81 (d, J = 9.2 Hz, 2H), 6.24 (s, 1H), 6.0 (t, J = 5.4 Hz, 1H), 4.34 (t, J = 5.6 Hz, 2H), 3.75 (m, 4H), 3.60 (t, J = 5.2 Hz, 2H), 3.25 (m, 4H), 2.37 (s, 3H), 2.12 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 405 $[M+H]^+$.

*3.1.58. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-1H-benzo[d][1,2,3] triazole-5-carboxamide (**8e**) (TG7-257)*

^{1}H NMR ($CDCl_3$+MeOH-d_4): δ 8.0 (s, 1H), 7.67 (s, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.24 (t, J = 4.4 Hz, 1H), 6.91 (m, 2H), 4.25 (t, J = 6.4 Hz, 2H), 3.62 (t, J = 6.4 Hz, 2H), 2.29 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 320 $[M+H]^+$.

*3.1.59. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxamide (**8f**) (TG7-207)*

^{1}H NMR (DMSO-d_6): δ 8.90 (t, J = 5.6 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.72 (s, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.38 (t, J = 6.8 Hz, 2H), 7.01 (t, J = 7.2 Hz, 1H), 6.9 (t, J = 7.2 Hz, 1H), 6.16 (s, 1H), 4.25 (t, J = 6.8 Hz, 2H), 3.52 (q, J = 6 Hz, 2H), 2.36 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 379 $[M+H]^+$.

*3.1.60. ^{t}Butyl 3-(4-((2-(2-methyl-1H-indol-1-yl)-ethyl)carbamoyl) phenyl)piperidine-1-carboxylate (**8g**) (TG7-264)*

^{1}H NMR ($CDCl_3$): δ 7.53 (d, J = 7.6 Hz, 2H)), 7.51 (d, J = 4.8 Hz, 1H), 7.31 (d, J = 8 Hz, 1H), 7.22 (d, J = 7.6 Hz, 2H), 7.08 (m, 2H), 6.06 (t, J = 6 Hz, 1H), 4.35 (t, J = 6 Hz, 2H), 4.13 (m, 2H), 3.78 (q, J = 6 Hz, 2H), 2.72 (m, 4H), 2.38 (s, 3H), 1.97 (m, 1H), 1.72 (m, 1H), 1.58 (m, 3H), 1.44 (s, 9H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 462 $[M+H]^+$.

*3.1.61. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-(piperidin-3-yl) benzamide (**8h**) (TG7-268)*

^{1}H NMR ($CDCl_3$): δ 7.47 (m, 3H)), 7.25 (dd, J = 7.6, 1.6 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.0 (m, 3H), 6.16 (d, J = 6 Hz, 1H), 4.33 (q, J = 6.2 Hz, 2H), 3.77 (q, J = 6.2 Hz, 2H), 3.30 (m, 1H), 3.11 (m, 1H), 2.72 (m, 1H), 2.32 (s, 3H), 1.80–1.60 (m, 6H). LCMS (ESI): >94% purity at λ 254, MS; m/z, 362 $[M+H]^+$.

*3.1.62. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-(piperidin-4-yloxy) benzamide (**8i**) (TG7-234)*

^{1}H NMR ($CDCl_3$): δ 7.53 (m, 2H)), 7.35 (m, 1H), 7.30 (d, J = 8 Hz, 1H), 7.10 (m, 1H), 6.85 (m, 3H), 6.24 (s, 1H), 6.06 (t, J = 5.6 Hz, 1H), 4.6 (broad singlet, 1H), 4.33 (q, J = 6.2 Hz, 2H), 3.77 (q, J = 6.2 Hz, 2H), 3.11 (m, 2H), 2.69 (m, 2H), 2.37 (s, 3H), 1.98 (m, 1H), 1.92 (m, 1H), 1.6 (m, 2H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 378 $[M+H]^+$.

*3.1.63. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-(morpholinomethyl) benzamide (**8j**) (TG8-5)*

^{1}H NMR ($CDCl_3$): δ 7.53 (t × d, J = 6.4, 1.6 Hz, 3H)), 7.34 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8 Hz, 1H), 7.08 (m, 2H), 6.25 (s, 1H), 4.35 (t, J = 6 Hz, 2H), 3.77 (q, J = 6 Hz, 2H), 3.69 (t, J = 4.4 Hz, 4H), 3.50 (s, 2H), 2.41 (broad singlet, 4H), 2.38 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 375 $[M+H]^+$.

*3.1.64. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (**8k**) (TG8-6)*

^{1}H NMR ($CDCl_3$): δ 7.52 (t × d, J = 6.4, 1.6 Hz, 3H)), 7.32 (m, 3H), 7.07 (m, 2H), 6.25 (s, 1H), 4.35 (t, J = 6 Hz, 2H), 3.77 (q, J = 6 Hz, 2H), 3.50 (s, 2H), 2.45 (broad singlet, 8H), 2.38 (s, 3H), 2.28 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 391 $[M+H]^+$.

*3.1.65. 2-Amino-N-(2-(2-methyl-1H-indol-1-yl)ethyl)pyrimidine-5-carboxamide (**8l**) (TG7-261)*

^{1}H NMR (DMSO-d_6): δ 8.55 (s, 2H), 8.47 (t, J = 6 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.18 (s, 2H), 6.99 (t, J = 6.8 Hz, 1H), 6.93 (t, J = 6.8 Hz, 1H), 6.16 (s, 1H), 4.23 (t, J = 6.8 Hz, 2H), 3.46 (q, J = 6.4 Hz, 2H), 2.34 (s, 3H). LCMS (ESI): >98% purity at λ 254, MS; *m*/*z*, 295 $[M+H]^+$.

*3.1.66. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-2-(phenylamino) pyrimidine-5-carboxamide (**8m**) (TG7-228)*

^{1}H NMR ($CDCl_3$+MeOH-d_4): δ 8.60 (s, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.28 (m, 2H), 7.04 (m, 3H), 6.19 (s, 1H), 4.27 (t, J = 6 Hz, 2H), 3.65 (t, J = 6 Hz, 2H), 2.33 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; *m*/*z*, 372 $[M+H]^+$.

*3.1.67. 2-(Ethylamino)-N-(2-(2-methyl-1H-indol-1-yl)ethyl) pyrimidine-5-carboxamide (**8n**)(TG7-229)*

^{1}H NMR ($CDCl_3$+MeOH-d_4): δ 8.47 (s, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.25 (d, J = 7.6 Hz, 1H), 7.04 (m, 2H), 6.21 (s, 1H), 4.29 (t, J = 6 Hz, 2H), 3.68 (q, J = 6 Hz, 2H), 3.41 (q, J = 7.2 Hz, 2H), 2.34 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H). LCMS (ESI): >98% purity at λ 254, MS; *m*/*z*, 324 $[M+H]^+$.

*3.1.68. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-2-morpholinopyrimidine-5-carboxamide (**8o**) (TG7-249)*

^{1}H NMR ($CDCl_3$): δ 8.59 (s, 2H), 7.50 (d, J = 7.6 Hz, 2H), 7.30 (d, J = 8 Hz, 1H), 7.09 (m, 2H), 6.24 (s, 1H), 6.05 (t, J = 4 Hz, 1H), 4.33 (t, J = 6 Hz, 2H), 3.89 (t, J = 4.8 Hz, 4H), 3.75 (q, J = 4.8 Hz, 4H), 2.38 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; *m*/*z*, 366 $[M+H]^+$.

*3.1.69. 2-Amino-N-(2-(2-methyl-1H-indol-1-yl)ethyl)nicotinamide (**8p**) (TG7-259)*

^{1}H NMR ($CDCl_3$): δ 8.0 (d, J = 5.2 Hz, 1H), 7.15 (d, J = 7 Hz, 1H), 7.28 (d, J = 8 Hz, 1H), 7.08 (m, 2H), 6.69 (broad singlet, 2H), 6.47 (dd, J = 7.8, 4.8 Hz, 1H), 6.26 (s, 1H), 6.15 (broad triplet, J = 7 Hz, 1H), 4.33 (t, J = 6 Hz, 2H), 3.74 (t, J = 6 Hz, 4H), 3.74 (q, J = 6 Hz, 2H), 2.39 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; *m*/*z*, 295 $[M+H]^+$.

*3.1.70. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-1-(pyrimidin-2-yl) piperidine-4-carboxamide (**8q**) (TG7-244)*

^{1}H NMR ($CDCl_3$): δ 8.29 (d, J = 4.8 Hz, 2H), 7.49 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.05 (m, 2H), 6.48 ((t, J = 5.6 Hz, 1H), 6.24 (s, 1H), 5.50 (broad triplet, J = 7 Hz, 1H), 4.74 (d, J = 16 Hz, 2H), 4.23 (t, J = 6 Hz, 2H), 3.58 (q, J = 6 Hz, 2H), 2.87 (t, J = 6 Hz, 2H), 2.39 (s, 3H), 2.21 (m, 1H), 1.79 (m, 2H), 1.59 (m, 2H). LCMS (ESI): >97% purity at λ 254, MS; *m*/*z*, 364 $[M+H]^+$.

*3.1.71. N-(2-(5-Fluoro-2-methyl-1H-indol-1-yl)ethyl)-4-morpholinobenzamide (**8r**) (TG7-183)*

^{1}H NMR ($CDCl_3$): δ 7.53 (dd, J = 7, 2 Hz, 2H), 7.21 (dd, J = 8.8, 4.4 Hz, 1H), 7.14 (dd, J = 9.6, 2.4 Hz, 1H), 6.82 (m, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.19 (s, 1H), 6.06 (t, J = 6 Hz, 1H), 4.3 (t, J = 6 Hz, 2H), 3.8 (t, J = 4.8 Hz, 4H), 3.73 (t, J = 6 Hz, 2H), 3.22 (t, J = 4. 8 Hz, 4H), 2.36 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; *m*/*z*, 382 $[M+H]^+$.

*3.1.72. 3-Fluoro-N-(2-(5-fluoro-2-methyl-1H-indol-1-yl)ethyl)-4-(4-methylpiperazin-1-yl)benzamide (**8s**) (TG7-184)*

^{1}H NMR ($CDCl_3$): δ 7.33 (dd, J = 13.6, 2 Hz, 1H), 7.25 (dd, J = 8.2, 2 Hz, 1H), 7.19 (dd, J = 8.8, 4.4 Hz, 1H), 7.13 (dd, J = 9.6, 2.4 Hz, 1H), 6.83 (m, 2H), 6.19 (s, 1H), 6.12 (t, J = 5.4 Hz, 2H), 4.29 (t, J = 6 Hz, 2H), 3.71 (q, J = 6 Hz, 2H), 3.16 (t, J = 4.8 Hz, 4H), 2.55 (t, J = 4.8 Hz, 4H), 2.35 (s, 3H), 2.32 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; *m*/*z*, 413 $[M+H]^+$.

*3.1.73. 4-(Diethylamino)-N-(2-(2-(trifluoromethyl)-1H-indol-1-yl) ethyl)benzamide (**8t**)(TG4-194)*

^{1}H NMR ($CDCl_3$): δ 7.64 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 7.2 Hz, 2H), 7.30 (t, J = 8.4 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 6.95 (s, 1H), 6.57 (d, J = 8.8 Hz, 2H), 6.07 (t, J = 5.6 Hz, 1H), 4.4 (t, J = 6.8 Hz, 2H), 3.78 (q, J = 6 Hz, 2H), 3.37 (q, J = 7.2 Hz, 4H), 1.63 (t, J = 6.8 Hz, 6H). LCMS (ESI): >97% purity at λ 254, MS; *m*/*z*, 404 $[M+H]^+$.

*3.1.74. 4-Morpholino-N-(2-(2-(trifluoromethyl)-1H-indol-1-yl) ethyl)benzamide (**8u**) (TG7-195)*

^{1}H NMR ($CDCl_3$): δ 7.65 (d, J = 8 Hz, 1H), 7.6 (d, J = 8.4 Hz, 1H), 7.57 (t, J = 7.2 Hz, 2H), 7.29 (t × d, J = 7.2, 1.2 Hz, 1H), 7.15 (t × d, J = 7.2, 1.2 Hz, 1H), 6.96 (s, NH), 6.82 (dd, J = 6.8, 1.2 Hz, 2H), 6.13 (t, J = 5.6 Hz, 1H), 4.49 (t, J = 6.4 Hz, 2H), 3.83 (q, J = 5.2 Hz, 4H), 3.81 (q, J = 6.4 Hz, 2H). LCMS (ESI): >97% purity at λ 254, MS; *m*/*z*, 418 $[M+H]^+$.

*3.1.75. 4-(Diethylamino)-N-(2-(2-methyl-1H-benzo[d]imidazol-1-yl)ethyl)benzamide (**8v**) (TG7-199)*

^{1}H NMR ($CDCl_3$): δ 7.64 (m, 1H), 7.53 (dd, J = 7.2, 2 Hz, 2H), 7.32 (m, 1H), 7.19 (m, 2H), 6.54 (d, J = 8.8 Hz, 2H), 6.4 (t, J = 6 Hz, 1H), 4.35 (t, J = 5.6 Hz, 2H), 3.75 (q, J = 5.6 Hz, 2H), 3.35 (q, J = 7.2 Hz, 4H), 2.43 (s, 3H), 1.14 (t, J = 7.2 Hz, 6H). LCMS (ESI): >97% purity at λ 254, MS; *m*/*z*, 351 $[M+H]^+$.

*3.1.76. N-(2-(1H-Benzo[d]imidazol-1-yl)ethyl)-4-(diethylamino) benzamide (**8w**) (TG7-203)*

^{1}H NMR ($CDCl_3$): δ 7.69 (d, J = 4 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 6.4 Hz, 1H), 7.23 (m, 2H), 6.66 (bs, 1H), 6.53 (d, J = 8.8 Hz, 2H), 4.38 (t, J = 5.2 Hz, 2H), 3.75 (q, J = 5.6 Hz, 2H), 3.54 (q, J = 7.2 Hz, 4H), 1.13 (t, J = 7.2 Hz, 6H). LCMS (ESI): >97% purity at λ 254, MS; *m*/*z*, 337 $[M+H]^+$.

*3.1.77. 4-Acetamido-N-(2-(2-methyl-1H-indol-3-yl)ethyl) benzamide (**8x**) (TG7-146)*

^{1}H NMR ($CDCl_3$): δ 7.4 (m, 4H), 7.22 (d, J = 9 Hz, 2H), 7.0 (m, 2H), 3.6 (t, J = 6.4 Hz, 2H), 2.95 (t, J = 6.4 Hz, 2H), 2.26 (s, 3H), 2.08 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; *m*/*z*, 336 $[M+H]^+$.

*3.1.78. N, N-Diethyl-N4-(2-(2-methyl-1H-indol-3-yl)-ethyl) terephthalamide (**8y**) (TG7-231)*

^{1}H NMR ($CDCl_3$): δ 7.61 (d, J = 8 Hz, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 1H), 7.06 (m, 2H), 6.25 (bs, 1H), 3.68 (q, J = 6 Hz, 2H), 3.51 (q, J = 6.8 Hz, 2H), 3.16 (q, J = 6.4 Hz, 2H), 3.01 (t, J = 6.8 Hz, 2H), 2.30 (s, 3H), 1.23 (broad triplet, J = 6.4 Hz, 3H), 1.05 (broad triplet, J = 6.4 Hz, 3H). LCMS (ESI): >97% purity at λ 254, MS; *m*/*z*, 378 $[M+H]^+$.

*3.1.79. 4-(Dimethylamino)-N-(2-(2-methyl-1H-indol-3-yl)ethyl) benzamide (**8z**) (TG7-167)*

^{1}H NMR ($CDCl_3$): δ 8.2 (s, 1H), 7.54 (m, 3H), 7.25 (dd, J = 7.2, 2.4 Hz, 1H), 7.08 (m, 2H), 6.57 (dd, J = 7, 1.6 Hz, 2H), 6.14 (t, J = 5.6 Hz, 2H), 3.65 (q, J = 6.8 Hz, 2H), 2.98 (m, 2H), 2.95 (s, 3H), 2.31 (s, 3H). LCMS (ESI): >95% purity at λ 254, MS; *m*/*z*, 322 $[M+H]^+$.

*3.1.80. 4-(Diethylamino)-N-(2-(2-methyl-1H-indol-3-yl)ethyl) benzamide (**9a**) (TG7-181)*

^{1}H NMR ($CDCl_3$): δ 8.05 (s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 7.4 Hz, 1H), 7.10 (m, 2H), 6.55 (d, J = 9.2 Hz, 2H), 6.0 (t, J = 5.4 Hz, 1H), 3.67 (q, J = 6.4 Hz, 2H), 3.36 (q, J = 6.8 Hz, 2H), 2.99 (t, J = 6.4 Hz, 2H), 2.35 (s, 3H), 1.14 (t, J = 7.2 Hz, 6H). LCMS (ESI): >97% purity at λ 254, MS; *m*/*z*, 350 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{23}N_3O$; C, 75.61; H, 7.79; N, 12.02; Found; C, 75.58; H, 7.72; N, 12.07.

*3.1.81. N-(2-(2-methyl-1H-indol-3-yl)ethyl)-4-(piperidin-1-yl) benzamide (**9b**) (TG7-168)*

^{1}H NMR ($CDCl_3$): δ 8.2 (bs, 1H), 7.51 (d, J = 7.6 Hz, 2H), 7.25 (d, J = 8 Hz, 1H), 7.08 (m, 2H), 6.78 (d, J = 8.8 Hz, 2H), 6.13 (bs, 1H), 3.65 (q, J = 6 Hz, 2H), 3.22 (t, J = 4.8 Hz, 4H), 2.98 (t, J = 6.4 Hz, 2H), 2.31 (s, 3H), 1.64 (m, 4H), 1.60 (m, 2H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 362 $[M+H]^+$.

*3.1.82. N-(2-(2-methyl-1H-indol-3-yl)ethyl)-4-morpholinobenzamide (**9c**) (TG7-174)*

^{1}H NMR (DMSO-d_6). δ 10.62 (s, 1H), 8.30 (t, J = 5.6 Hz, 1H), 7.70 (d, J = 8.8 Hz, 2H)), 7.44 (d, J = 7.6 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 6.9 (m, 4H), 3.7 (t, J = 4.4 Hz, 4H), 3.34 (q, J = 6.4 Hz, 2H), 2.82 (q, J = 5.6 Hz, 2H), 2.46 (m, 4H), 2.26 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 364 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{25}N_3O_2$, C, 72.70; H, 6.93; N, 11.56; found, C, 72.31; H, 6.84; N, 11.48.

*3.1.83. 3-Fluoro-N-(2-(2-methyl-1H-indol-3-yl)ethyl)-4-morpholinobenzamide (**9d**) (TG7-175)*

^{1}H NMR (DMSO-d_6): δ 10.65 (s, 1H), 8.48 (t, J = 5.6 Hz, 1H), 7.59 (m, 2H)), 7.42 (d, J = 7.6 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 6.91 (m, 2H), 3.71 (t, J = 4.4 Hz, 4H), 3.34 (q, J = 6.4 Hz, 2H), 3.05 (t, J = 4.4 Hz, 4H), 2.82 (t, J = 7.6 Hz, 2H), 2.25 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 382 $[M+H]^+$.

*3.1.84. N-(2-(2-methyl-1H-indol-3-yl)ethyl)-4-(4-methylpiperazin-1-yl)benzamide (**9e**) (TG7-169)*

^{1}H NMR (DMSO-d_6): δ 8.2 (t, J = 5.2 Hz, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 8 Hz, 1H), 6.91 (m, 5H), 3.31 (q, J = 8 Hz, 2H), 3.20 (t, J = 4.8 Hz, 4H), 2.81 (t, J = 7.6 Hz, 2H), 2.39 (t, J = 4.8 Hz, 4H), 2.26 (s, 3H), 2.18 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 377 $[M+H]^+$.

*3.1.85. 2-(Ethylamino)-N-(2-(2-methyl-1H-indol-3-yl)ethyl) pyrimidine-5-carboxamide (**9f**) (TG7-232)*

^{1}H NMR ($CDCl_3$ + MeOH-d_4): δ 8.58 (broad singlet, 1H), 8.47 (bs, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.24 (m, 1H), 7.03 (m, 2H), 6.51 (broad singlet, 1H), 3.60 (q, J = 6.4 Hz, 2H), 3.40 (q, J = 7.2 Hz, 4H), 2.93 (t, J = 6.4 Hz, 2H), 2.31 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 324 $[M+H]^+$.

*3.1.86. N-(2-(2-methyl-1H-indol-3-yl)ethyl)-2-morpholinopyrimidine-5-carboxamide (**9g**) (TG7-8-9)*

^{1}H NMR ($CDCl_3$): δ 8.58 (s, 2H), 7.43 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 8 Hz, 1H), 7.01 (m, 2H), 3.78 (t, J = 5.2 Hz, 4H), 3.67 (t, J = 5.2 Hz, 4H), 3.55 (t, J = 6.8 Hz, 2H), 2.93 (t, J = 6.4 Hz, 2H), 2.28 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 366 $[M+H]^+$.

*3.1.87. 5-Fluoro-N-(2-(2-methyl-1H-indol-1-yl)ethyl)-1H-benzo[d] imidazole-2-carboxamide (**9h**) (TG7-118)*

^{1}H NMR (DMSO-d_6): δ 9.2 (t, J = 4 Hz, 1H), 7.45 (d, J = 8 Hz, 1H), 7.36 (d, J = 7.6 Hz, 2H), 7.13 (t, J = 9.6 Hz, 1H), 6.99 (t, J = 6.8 Hz, 1H), 6.19 (t, J = 6.8 Hz, 1H), 6.14 (s, 1H), 4.27 (t, J = 6.8 Hz, 2H), 3.55 (q, J = 6.8 Hz, 2H), 2.38 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 337 $[M+H]^+$.

*3.1.88. 6-Fluoro-4-hydroxy-N-(2-(2-methyl-1H-indol-1-yl)ethyl) quinoline-3-carboxamide (**9i**) (TG7-148)*

^{1}H NMR (DMSO-d_6): δ 7.84 (dd, J = 9, 2.8 Hz, 1H)), 7.75 (dd, J = 9.4, 4.4 Hz, 1H), 7.66 (t × d, J = 8, 2.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.0 (t, J = 7.2 Hz, 1H), 6.92 (t, J = 7.2 Hz, 1H), 6.14 (s, 1H), 4.25 (t, J = 6.8 Hz, 2H), 3.60 (q, J = 6.4 Hz, 2H), 2.37 (s, 3H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 364 $[M+H]^+$.

*3.1.89. N-(2-(2-methyl-1H-indol-1-yl)ethyl)-5-oxopyrrolidine-2-carboxamide (**9j**) (TG7-120)*

^{1}H NMR ($CDCl_3$): δ 7.47 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 8 Hz, 1H), 7.10 (t, J = 7.2 Hz, 1H), 7.02 (t, J = 6.8 Hz, 1H), 6.52 (bs, 1H), 6.23 (bs, 1H), 5.68 (bs, 1H), 4.2 (m, 2H), 3.9 (m, 1H), 3.59 (m, 2H), 2.41 (s, 3H), 2.35 (m, 1H), 2.09 (t, J = 8 Hz, 1H), 1.9 (m, 2H). LCMS (ESI): >95% purity at λ 254, MS; m/z, 286 $[M+H]^+$.

*3.1.90. 4-(Diethylamino)-N-(3-(2-methyl-1H-indol-1-yl)propyl) benzamide (**9k**) (TG7-200)*

^{1}H NMR ($CDCl_3$): δ 7.51 (d, J = 7.6 Hz, 1H), 7.44 (m, 2H), 7.26 (d, J = 8 Hz, 1H), 7.12 (t, J = 8 Hz, 1H), 7.05 (t, J = 8 Hz, 1H), 6.56 (d, J = 7.2 Hz, 2H), 6.23 (s, 1H), 5.76 (t, J = 5.2 Hz, 1H), 4.18 (t, J = 6.2 Hz, 2H), 3.43 (q, J = 6.2 Hz, 2H), 3.78 (q, J = 7.2 Hz, 4H), 2.41 (s, 3H), 2.06 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 6H). LCMS (ESI): >98% purity at λ 254, MS; m/z, 364 $[M+H]^+$.

*3.1.91. 4-Morpholino-N-(2,3,4,9-tetrahydro-1H-carbazol-3-yl) benzamide (**9l**) (TG8-17-2)*

^{1}H NMR ($CDCl_3$): δ 7.57 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8 Hz, 1H), 7.21 (d, J = 8 Hz, 1H), 7.01 (t, J = 7.2 Hz, 1H), 6.95 (t, J = 7.2 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 6.56 (t, J = 7.6 Hz, 1H), 4.47 (m, 1H), 3.75 (t, J = 4.8 Hz, 4H), 3.13 (t, J = 4.8 Hz, 4H), 3.06 (dd, J = 15.6, 5.2 Hz, 2H), 2.77 (m, 2H), 2.63 (dd, J = 15.6, 6.4 Hz, 1H), 2.05 (m, 2H). LCMS (ESI): >97% purity at λ 254, MS; m/z, 376 $[M+H]^+$.

*3.1.92. (3-(2-Methyl-1H-indol-1-yl)piperidin-1-yl)(4-morpholinophenyl)methanone (**9m**) (TG7-292)*

^{1}H NMR ($CDCl_3$): δ 7.80 (s, 1H), 7.60 (d, J = 6.2 Hz, 1H), 7.40 (d, J = 6.2 Hz, 1H), 7.26 (m, 1H), 7.08 (m, 3H), 6.90 (m, 2H), 3.84 (broad singlet, 4H), 3.15 (broad singlet, 4H), 2.80 (m, 2H), 2.40 (s, 3H), 2.37 (m, 3H), 2.19–2.13 (m, 2H), 2.00 (m, 2H). Note: The peaks were not clean. LCMS (ESI): >80% purity at λ 254, MS; m/z, 404 $[M+H]^+$.

*3.1.93. 2-(2-Methyl-1H-indol-1-yl)ethyl 4-(diethyl-amino)benzoate (**9n**) (TG7-208)*

^{1}H NMR ($CDCl_3$): δ 7.70 (d, J = 8 Hz, 2H), 7.50 (d, J = 8 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 6.56 (d, J = 8 Hz, 2H), 6.25 (s, 1H), 4.51 (t, J = 6.2 Hz, 2H), 4.41 (t, J = 6.2 Hz, 2H), 3.39 (q, J = 7.2 Hz, 4H), 2.45 (s, 3H), 1.17 (t, J = 7.2 Hz, 6H). LCMS (ESI): >98% purity at λ 254, MS; m/z, 351 $[M+H]^+$.

3.2. Assay description

The development of C6-glioma cells overexpressed with EP2, EP4 and DP1 and IP receptors, TR-FRET bioassay was carried out as previously described [19,20,32,33].

Author contributions

T.G. and R.D. designed the research. T.G. and J.J. performed the research. T.G. wrote the manuscript and R.D. helped with the writing.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.05.076.

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